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***Nuclear Medicine in
Thyroid Cancer Management:
A Practical Approach***



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FOREWORD

Thyroid cancers are now being diagnosed at an earlier stage and treatments together with follow-up strategies are more effective. However this is not consistent throughout the world. The practice does differ considerably from country to country and region to region. Many International Atomic Energy Agency (IAEA) Members States can benefit from the lessons learned and improve overall patient management of thyroid cancers.

The IAEA has significantly enhanced the capabilities of many Member States in the field of nuclear medicine. Functional imaging using nuclear medicine procedures has become an indispensable tool for the diagnosis, treatment planning and management of patients. In terms of treatment, the use of radioiodine (^{131}I) has been central to thyroid cancer and has been successfully used for over six decades. Over the years the IAEA has also assisted many Member States to develop indigenous manufacturing of radioiodine therefore reducing the barriers for the care of patients.

This publication is a culmination of efforts by more than twenty international experts in the field to produce a global perspective on the subject. Views expressed are those of individual experts involved and are intended to assist national or regional authorities in decisions regarding the frameworks for effective treatment of thyroid cancer.

The IAEA is grateful to all the contributors and reviewers. The IAEA officers responsible for this publication were, in chronological order, A.K. Padhy, M. Dondi and K.K. Solanki. The IAEA officer responsible for revising and finalizing this publication was K.K. Solanki of the Division of Human Health.

EDITORIAL NOTE

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1. EPIDEMIOLOGY AND AETIOLOGY

1.1. Background

This book is based on series of IAEA technical consultations mainly in the early part of this millennium. These technical consultations were than pooled together into a single IAEA publication with additional sections added to reflect current practice such as the use of thyroglobulin monitoring with the aid and services of international consultants. It provides views and practices from an international perspective, and the views expressed are those of individual experts involved. The publication is of directed at nuclear physicians, radiologists, oncologists, surgeons (general and head and neck surgeons), endocrinologists, medical physicists, medical technologists, radiopharmacists, radiotherapists, laboratory medicine scientists and researchers.

1.1.1. Objective

The prime objective of this book is to provide views and practices from an international perspective, thus an overview of thyroid cancer from series of technical consultations on nuclear medicine practices.

1.1.2. Scope

This publication can support essential discussion aimed at assisting the process of standardization and harmonization of clinical practice. This publication assists with the process of review and decision-making. It provides suggestions on improving numerous protocols leading to better patient management.

1.1.3. Structure

The structure takes the reader from primary care interventions, to diagnostic strategies, to widespread use of fine-needle aspiration biopsy, to surgery and to treatment options. It discusses clinical evaluation, management and long term follow-up of thyroid cancer patients. It provides specific information on the main goal of long term follow-up and detection of recurrent disease. It also deals with the combined use of thyroglobulin monitoring and recombinant human thyroid stimulating hormones (rhTSH) in modern day practices.

1.2. Epidemiology of thyroid cancer: global scenario

Although thyroid nodules are common, thyroid cancer is relatively rare. The overall incidence of cancer in a cold nodule is 5% to 15%, but it is higher in patients at the extremes of age. Clinically detectable thyroid carcinomas constitute less than 1 per cent of all human cancers. The annual incidence rate in various parts of the world ranges from 0.5 to 10 cases per 100 000 population [1.1-1.6]. Hawaii, has the highest rate for thyroid cancer in both sexes. Globally, the lowest rate reported was from Barshi, India where the rate was 0.2/100 000 for females. Among males, in 174 out of 183 populations examined, the annual incidence rates were below 3 per 100 000 and among females the rates were below 5 per 100 000 in 123 out of 183 population groups [1.2].

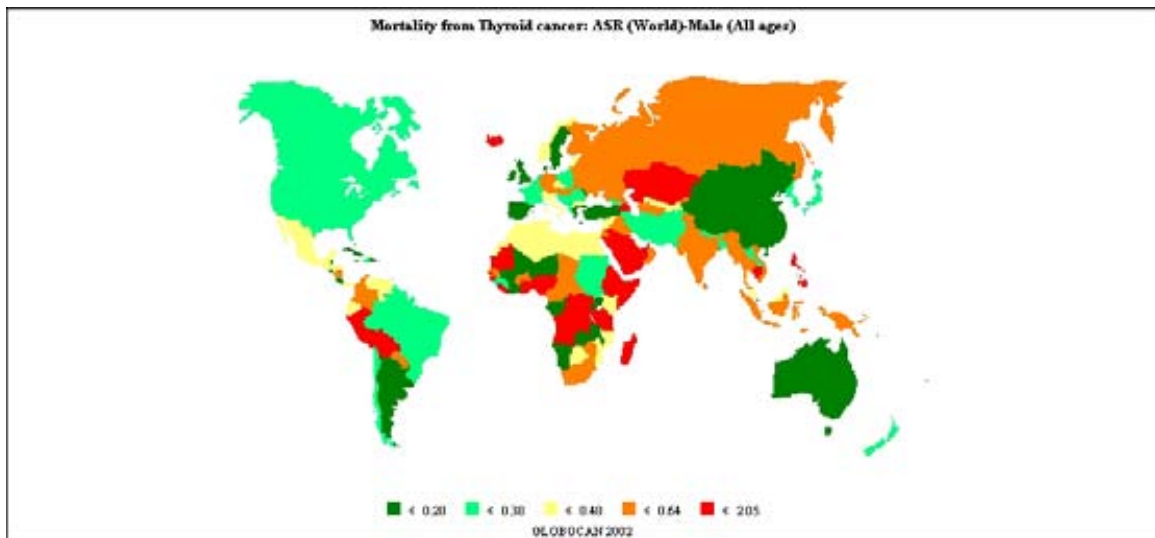


FIG. 1.1. Mortality from thyroid cancers — male.

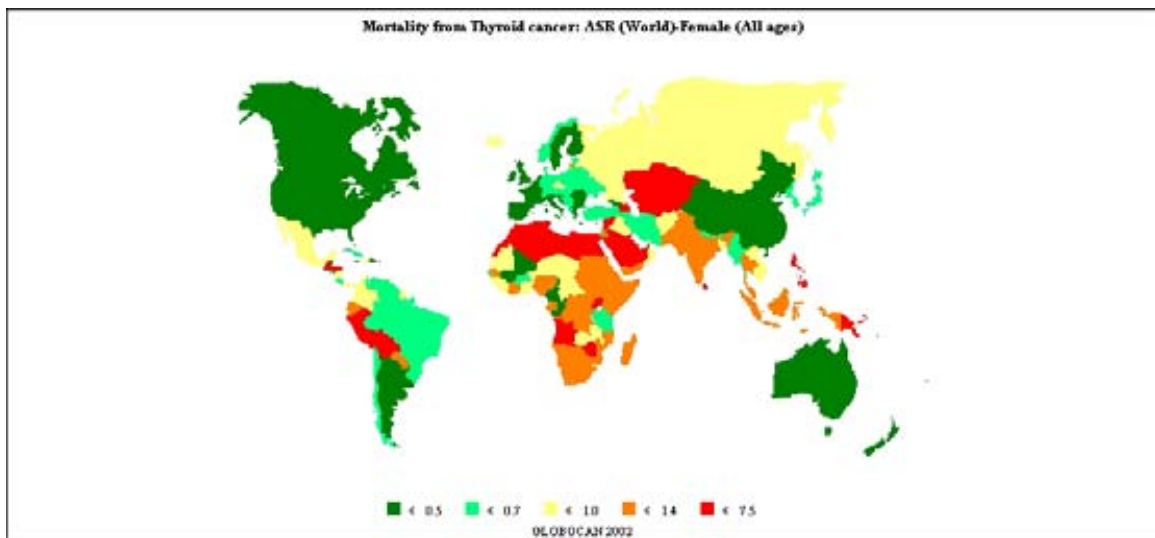


FIG. 1.2. Mortality from thyroid cancers — female.

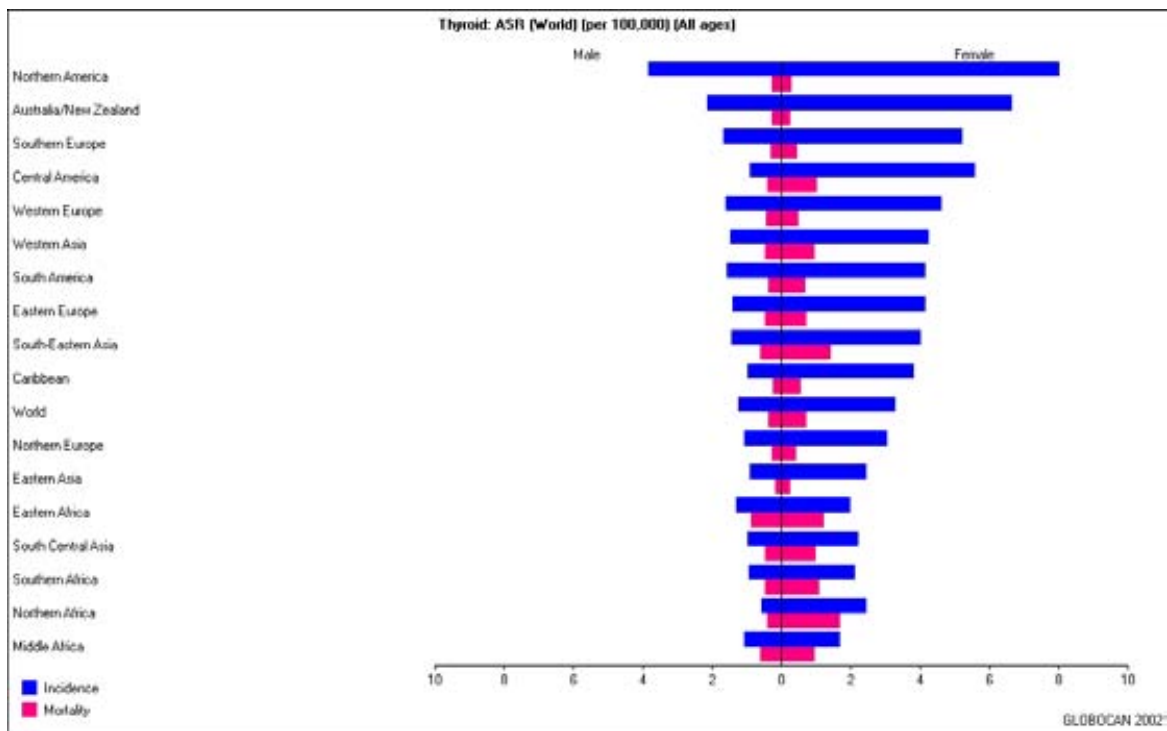


FIG. 1.3. Incidence and mortality — thyroid cancers.

Age standardised rate (ASR) in females were always higher than in males in all countries as depicted in ‘Gobocan 2002’ (Figs 1.1, 1.2, 1.3). The rates in females were more than twice the rates in males in most of the population studied [1.1]. In Europe, France (11.06), Romania (9.09), Italy (9.3) and Iceland (9.80) have the highest rates in females. A high incidence of thyroid cancer has been observed in Iceland and in native Alaskan women also. Among men the highest rate was seen in Iceland (6.06) followed by Filipinos in Hawaii 5.08, and the Non Kuwaitis in Kuwait (4.79). Filipino men also have rates higher than most other groups [1.6].

An increasing trend in incidence has been observed especially in females in the United States of America (USA), Japan, Finland and Singapore and Chinese populations, whereas in India and the United Kingdom (UK) the rates have remained steady over the past 30 years. However, the analysis of incidence data from Connecticut, USA between 1935-1939 and 1990-1992 indicated that the increase in the incidence was due to cohort effect. The increase was observed in the cohort born between 1915 and 1945. For those born after 1945 the incidence declined. This was attributed to the practice of ionising radiation treatment for benign childhood conditions such as acne, parasitic infections of the scalp, and cervical adenitis. [1.3].

Cancer of thyroid in children has been observed and reported from all over the world. Though its incidence is low throughout the world, it has provided a base to study the aetiology of this disease. Parkin, et al. [1.4] have collected data on children from both population based registries and from established hospitals in the world in a book on childhood cancer where over 50 countries which includes regions from Africa, North America (USA and Canada), South America (Brazil, Columbia, Cuba, Jamaica, Puerto Rico), Asia (15 countries), Europe (22 countries) and Oceania (Australia, New Zealand and Fiji) were analysed. The highest ASR's for thyroid cancer in children among females were reported from African Americans in Los Angeles, USA with a rate of 2.8 per million and among males from the non Jewish population in Israel at 2.3 per million. Further the ASR's were higher in females than in

males. It was observed in 33 out of the 65 populations where the rate in females was about one to five times higher than that in males.

Religious and ethnic differences in the incidence of thyroid cancer have also been reported in the literature [1.5-1.9]. In USA the rates in both sexes amongst non-African Americans were higher than that among African Americans population. In Israel, all the Jewish population had higher rates for thyroid cancer than other religious groups and the differences did not relate to their place of birth. Singaporean Malays have a higher incidence rate of thyroid cancer (males = 2.7, females = 5.0) than Singaporean Chinese (males = 1.5, females = 4.3) and the Singaporean Indian population (males = 0.7, females = 1.1). There have been very little differences in the incidence of thyroid cancer in the Japanese and Chinese who migrated to the USA, except for those who settled in Hawaiian island, where there was an increase in the incidence of thyroid cancer in both sexes as compared to the population of the country of origin [1.6]. The highest age adjusted incidence rate (AAR) of thyroid cancer was seen among Filipino women in Hawaii (ASR 25.46/100 000) followed by women residing in French Polynesia (15.9/100 000). Almost all communities living in Hawaii have rates higher than that seen in other areas of the world. This is seen both among males and females. However, women living in Manila, have incidence rates (8.7/100 000) one third of the rates seen in Filipinos of Hawaii. Similarly Chinese women in China have very low rates, between 0.5 and 2.96 but in Hawaii, Chinese women have an incidence rate of 9.42 [1.9]. Though many cancers are known to differ according to urban/rural status, there has not been any study to indicate this in the case of thyroid cancer.

1.3. Aetiology and risk factors

A risk factor is anything that increases a person's chance of getting a disease such as cancer. Different cancers have different risk factors. For example, unprotected exposure to strong sunlight is a risk factor for skin cancer, and smoking is a risk factor for cancers of the lungs, mouth, throat, oesophagus, bladder, and several other organs. Several authors have found a few risk factors that make a person more likely to develop thyroid cancer. However, even if a patient with thyroid cancer has one or more risk factors, it is impossible to know exactly how much that risk factor may have contributed to causing the cancer.

Of the few factors that are suspected as high risk for thyroid cancer are (a) exposure to radiation, (b) iodine intake and (c) certain diets. Of these, radiation exposure has been regarded as consistent with a causal role for thyroid cancer. Therapeutic radiation, radiation fall out from nuclear weapon testing and radiations from nuclear accidents have been observed as risk factors.

1.3.1. Radiation related risk factors

Natural high background radiation, Radiation exposures due to diagnostic, therapeutic, or accidental exposures

Low-level radiation like the high natural background radiation has not yet been shown as a high risk factor. An early study of resected specimens of thyroid nodules from people residing in the high natural radiation area of Kerala, India and a comparable control series did not indicate an increased frequency of thyroid cancer [1.12]. A study from the high natural radiation area in China has also shown similar results [1.13]. Natural high background radiation has been observed in the Karunagapally area of Quilon District in Kerala, India. The place is known for its monazite deposit, which emits gamma radiation varying from

3.8 mGy/a to 35 mGy/a [1.14]. Data indicates a high incidence of thyroid cancer in this area compared to others in India. However in the city of Thiruvananthapuram, 100 km away from Karunagappally, there is higher incidence of thyroid cancer in both sexes. Therefore, the association between risk for cancer and geographic variations in natural background radiation remains equivocal.

Exposure of the head and neck to radiation in early childhood increases the frequency of benign and malignant lesions. It is the only established etiological factor for thyroid cancer. The effect of radiation is more marked in the younger age group, as evident by the increased incidence in children three years after the nuclear accident in Belarus [1.15,1.16].

As a result of the accident at the Chernobyl Nuclear Power Plant on 26 April 1986, millions of Curies of short lived radioiodine isotopes were released in the fallout. The absorption of radioiodine through ingestion of contaminated food and water and inhalation led to an exposure of the thyroid gland that was 3-10 times higher in children than in adults. The risk of thyroid cancer was inversely correlated with the distance of residence from the source of contamination and age at the time of exposure. In children exposed to therapeutic radiation the incidence (33-37%) has been higher than that in non-exposed children [1.17-1.18].

A post Chernobyl rise in thyroid cancer was observed in far off places like Connecticut, in children as well as in adults, 4-7 years after the accident. This phenomenon was seen in other states like Iowa and Utah [1.20]. More details on the effect of radiation releases after Chernobyl accident is being described under various links from IAEA web site on Chernobyl forum.

1.3.2. Genetic factors

The mechanism by which radiation induces thyroid cancer at a low dose is not clear. It may be because of rearrangement of *ret* protooncogene due to the aberrant expression of the tyrosine kinase domain of the receptor involved in thyroid carcinogenesis [1.21]. However, the *ret* oncogene rearrangement is also found in tumours from non-irradiated children. Radiation may cause DNA strand break, which if not repaired can remain dormant and may express later if triggered by 'modifier genes' or other tumour promoting agents such as environmental factors, free radicals or hitherto other unknown factor(s) [1.22-1.25]. Analysis of thyroid cancer data from the Ukraine after Chernobyl using a two-mutation carcinogenesis model indicated that the absolute excess radiation risk per unit dose for children is about the same as or a little lower than that for adults [1.25]. Details on the genetic effects on thyroid cancer are presented in another section.

1.3.3. Hereditary conditions

People with certain inherited medical conditions are also at higher risk of thyroid cancer. Higher rates of the disease occur among people with conditions called Gardner's syndrome and familial polyposis. These conditions cause a very high risk of colorectal cancer and a slightly increased risk of cancers in some other organs. Also linked to an increased risk of thyroid cancer is Cowden's disease, a rare genetic condition. About 20% of medullary thyroid carcinomas result from inheriting an abnormal gene. These cases are known as familial medullary carcinoma. The combination of familial medullary thyroid carcinoma and tumours of other endocrine glands is called multiple endocrine neoplasia type 2 (MEN 2).

1.3.4. Iodine intake in diet

The role of iodine intake in preventing or promoting thyroid cancer has not been adequately demonstrated [1.26-1.29]. There is speculation of the role of dietary iodine in the increased incidence of thyroid cancer in Hawaiian populations where seafood is a predominant dietary constituent. However, there are reports that populations with iodine deficiency developed goitre and that such populations are seen to have more of the follicular type of thyroid cancer [1.27]. Iodine rich areas and iodine supplementation have shown an increase of papillary cancer (PC). In the coastal areas of Kerala, like Hawaii consumption of seafood is high and this could be a factor in the predominance of the PC in these areas as compared to the increase of follicular cancer (FC) in the areas remote from the coastal areas. A recent analysis relating iodine intake and thyroid cancer amongst women in a multiethnic population in the San Francisco Bay area study found that increased iodine intake was associated with a decreased risk of papillary thyroid cancer in low risk women but was slightly increased in high risk group of women with a history of goitre, nodules, family history of proliferative thyroid disease and those with history of radiation given to the head and neck. [1.30]. Another study from USA of a pooled analysis of the effect of fish and shell-fish consumption concluded that high consumption of fish did not increase the risk of developing thyroid cancer [1.31]. A review of available data from epidemiological studies, animal experiments and basic gene transfection studies indicated the relationship of iodine intake and cancer was poor [1.32].

1.3.5. Dietary goitrogens

The use of goitrogenic vegetables has also been suspected to increase the risk of thyroid cancer [1.31-1.34]. The consumption of cassava in Kerala, India is often mentioned in this regard. However, there are no studies reported yet which show that cassava consumption increases the risk of thyroid cancer. Cassava consumption is relatively more in men, especially in agricultural and farm labourers whose practice of eating fish and cooked cassava is believed to provide them the day's energy requirement. The female preponderance of thyroid cancer is thus not consistent with the suspected etiological role of cassava in thyroid cancer. The relation of phytosteroids and thyroid cancer risk was evaluated by San Francisco Bay Area group who suggested that ingestion of phytosteroids by modifying the diet to include soy and other phytosteroid foods could reduce the risk of thyroid cancers [1.35].

1.3.6. Hormonal factors

Female preponderance of thyroid cancer, the occurrence of thyroid cancer and breast cancer in a single individual, history of increased abortion among thyroid cancer patients have all led to theories related to the role of the female hormonal factor in the aetiology of thyroid cancer [1.5]. Adequate data is not yet available to explain the hypothesis.

1.3.7. Associated thyroid disorders

A history of benign thyroid diseases has also been associated with a higher risk of thyroid cancers [1.37-1.40]. The relative risk (RR) is 6-10 times for goitre, 13-33 for adenomas, 2.8-4.4 for thyroiditis. Patients with autoimmune thyroiditis are considered to be at high risk (80 times) for developing malignant lymphoma of the thyroid as compared to controls [1.39]. No significant risk has been reported for hypothyroidism.

Risk stratification has been higher in women younger than 55 years for benign and malignant thyroid disorders, being 16 for adenoma and 7 for goitre. Benign thyroid disorders are less common after the 6th decade indicating the importance of age.

Thyroid cancer is found in 5-8.7% of Graves' disease [1.41-1.44]. Analogous to TSH as a growth factor for thyroid cancer, thyroid stimulating immunoglobulins are believed to promote the growth of thyroid cancer [1.44]. Therapy with antithyroid drugs or radioiodine does not per se predispose to development of thyroid cancer. Cancer coexisting with Graves' disease is reported by some to be aggressive while others find no difference in the biological behaviour of the two diseases. These differences have been attributed to selection bias, geographical location (iodine deficiency) [1.40], genetic predisposition [1.45, 1.46] and environmental factors such as exposure to radiation in early childhood. Recently, Hayes, et al. has described four cases with toxic nodular goitre and thyroid cancer having an aggressive course of disease [1.42].

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2. CLASSIFICATION OF THYROID CANCER

Malignant neoplasms of the thyroid gland may be epithelial or non-epithelial. The epithelial tumours arise either from follicular cells or from parafollicular C cells, while the various sarcomas and malignant lymphomas comprise the non-epithelial tumours. The main pathologic features and biologic behaviour will be reviewed, including ancillary procedures which may aid in the histological typing of problematic cases. Histopathology and immunohistochemistry of thyroid cancer are important in the actual classification.

2.1. Classification of thyroid cancer

- Epithelial
 - Tumours with follicular cell differentiation
 - Follicular carcinoma
 - Minimally invasive
 - Widely invasive
 - Hurthle cell tumour
 - Papillary carcinoma
 - Conventional
 - Variants
 - Poorly differentiated
 - Insular carcinoma
 - Undifferentiated (anaplastic) carcinoma
 - Tumours of parafollicular or C cells
 - Medullary carcinoma
- Non-epithelial
 - Sarcomas
 - Malignant lymphomas

2.2. Follicular carcinoma

Follicular carcinoma is a malignant epithelial tumour that shows follicular cell differentiation not belonging to any other distinctive type of thyroid malignancy [2.1]. These are more common in iodide-deficient areas, where they make up 25 to 40% of thyroid cancers. Not all tumours which form follicles should be classified under this category, because of differences not only in morphologic features, but also in biologic behaviour. For example, some variants of papillary carcinoma exhibit follicular structure, but pursue a clinical course similar to conventional papillary carcinoma. Some authors consider oncocytic carcinoma separate from the usual follicular carcinoma. These will be described in subsequent sections.

There are two types of follicular carcinoma: minimally invasive and widely invasive [2.2, 2.3].

Minimally invasive follicular carcinoma is indistinguishable grossly from follicular adenoma. It presents as a solitary, well circumscribed nodule with a complete, usually thick capsule and a homogeneous, bulging, grey cut surface (Fig. 2.1). Histologically, the neoplasm composed of uniform small follicles. Diagnosis of malignancy requires demonstration of

capsular or vascular invasion (Fig. 2.2). For this reason, it cannot be diagnosed by fine needle aspiration biopsy. Full thickness invasion of the capsule is necessary to fulfil the criterion of capsular invasion. Indeed, some require tumour penetration or infiltration through the capsule [2.4]. At least 10 blocks are recommended to be taken around the nodule that will include the capsule and surrounding thyroid tissue. Vascular invasion should also be critically assessed — the intravascular tumour cells must show attachment to the endothelial surface, either partially or completely occluding the vessel lumen. The overall prognosis is excellent with a cure rate of 95% [2.5].

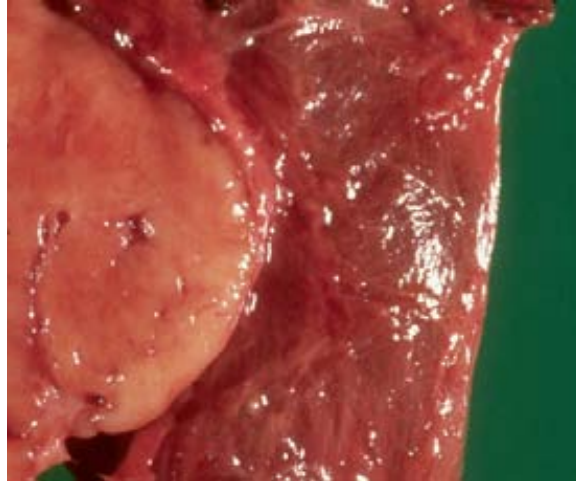


FIG. 2.1. Minimally invasive follicular carcinoma. The solitary, well circumscribed nodule shows a tan grey, bulging cut surface.

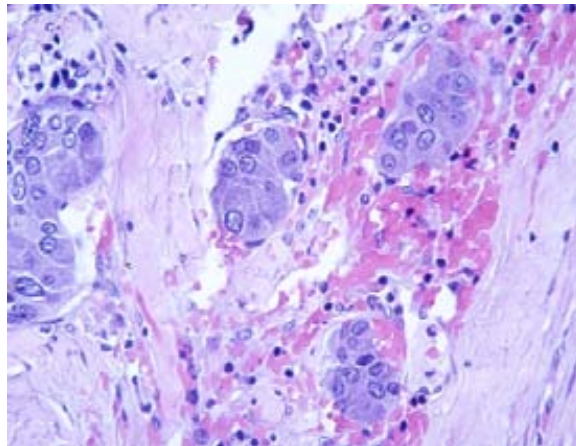


FIG. 2.2. Vascular invasion. Neoplastic follicular cells occurring in sheets within endothelium-lined spaces.

Widely invasive follicular carcinoma grossly exhibits extensive invasion of the surrounding tissue (Fig. 2.3). Microscopically, these tumours tend to be more obviously malignant than the minimally invasive category. Nuclear pleomorphism is usually evident, mitotic activity is prominent, and necrosis is more likely to be present. Mortality rate approaches 20% [2.4, 2.6].

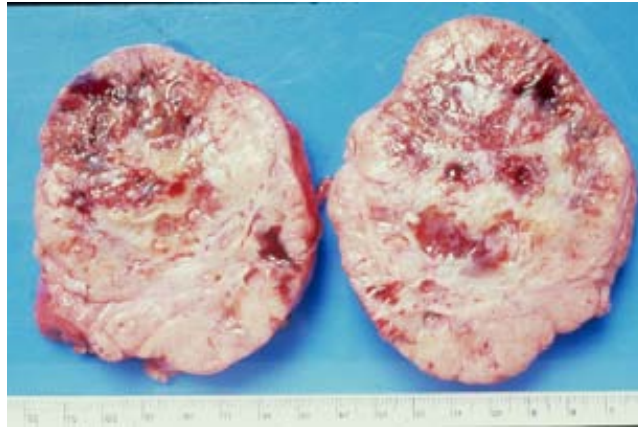


FIG. 2.3. Widely invasive follicular carcinoma. Necrosis and hemorrhage are evident in the cut surfaces.

Hurthle cell tumour. Hurthle cells or ‘oncocytic cells’ are transformed large follicular cells with abundant eosinophilic and granular cytoplasm, large nuclei, and prominent nucleoli. They can be seen in many thyroid lesions, including nodular goitre, Hashimoto’s thyroiditis, non-specific chronic thyroiditis, and follicular neoplasms. Neoplasms composed of Hurthle cells are still controversial with regard to their classification and biologic behaviour. Some consider it a subtype of follicular neoplasm and the criteria for differentiating benign from malignant are the same as in the other follicular tumours, including demonstration of invasion. [2.3]. Others, however, consider thyroid neoplasms composed of this cell type as a separate entity with different pathologic and behavioural features [2.1]. Most studies recognize benign and malignant forms, with invasion as the most important determining factor.

2.3. Papillary carcinoma

Papillary carcinoma is the most common type of thyroid cancer. In children, it constitutes 90% of all thyroid carcinomas [2.7]. It is a malignant epithelial tumour with evidence of follicular cell differentiation forming papillae and/or a set of distinctive nuclear features [2.1]. Prognosis is excellent, approaching 90% at 20 years [2.8]. The tumour is multifocal in 18-22% of cases, and metastasizes more frequently to regional cervical lymph nodes than to distant sites [2.8].

Grossly, the papillary nature of the tumour may be suspected from the granular surface (Fig. 2.4). The margins are ill-defined, and calcifications are indicated by a gritty sensation imparted to the cutting knife.



FIG. 2.4. Cut surface of papillary carcinoma. The coarsely granular surface reflects the microscopic morphologic features of branching processes.

Microscopically, there are two distinctive features of papillary carcinoma: papillary processes lined by columnar epithelium supported by thin, delicate fibrovascular stalks, and characteristic nuclear changes consisting of nuclear clearing and/or nuclear grooving [2.9] (Fig. 2.5). Psammoma bodies may be seen in association with the papillary fronds.

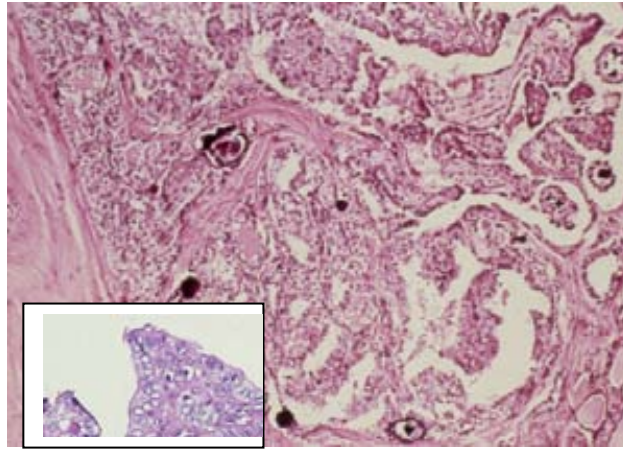


FIG. 2.5. Papillary carcinoma. Branching processes composed of fibrovascular stalks supporting low columnar cells with optically clear nuclei (inset). Psammoma bodies are also evident.

2.4. Papillary carcinoma variants

Occult sclerosing papillary tumour (papillary microcarcinoma). To be classified under this category, most pathologists agree that the papillary neoplasm should measure 1 cm. or less. Grossly, the lesion is a non-encapsulated grey nodule. It may show a totally follicular or a mixed follicular and papillary architecture, with the distinctive nuclear characteristics of papillary carcinoma. Like conventional papillary carcinoma, cervical lymph node metastases are common, and the nodal metastases may show a more obvious papillary pattern.

Follicular variant. This tumour exhibits a total or almost total follicular pattern, but with 'clear' or grooved nuclei. Most cases share many features of classic papillary carcinoma, including multicentric occurrence and its propensity to metastasize to cervical lymph nodes. However, some behave in an aggressive manner, metastasizing through the haematogenous route to distant sites [2.10].

Tall cell and columnar cell variants. The tall cell variant of papillary carcinoma makes up approximately 10% of thyroid cancers, tend to occur in the older age group, and is usually large (more than 5 cm.). The papillae are lined by cells that are twice as tall as they are wide, containing abundant eosinophilic cytoplasm superficially resembling oncocytes. This variant has a more aggressive clinical behaviour than the classic papillary thyroid carcinoma [2.11, 2.12].

The **columnar cell variant** differs from the tall cell variant from the presence of nuclear stratification. It may show clearing of the cytoplasm resembling subnuclear vacuolation in early secretory phase endometrium.

Diffuse sclerosing variant. This subtype of papillary carcinoma is characterized by a diffuse involvement of one, or more commonly both, lobes of the thyroid gland by multiple papillary formations within intrathyroid spaces probably representing lymphatic spaces, with tendency to be associated with squamous metaplasia, and many psammoma bodies. In contrast to the

conventional papillary carcinoma, this variant has a higher incidence of cervical nodal metastasis, a greater incidence of pulmonary metastasis, and a lesser probability of disease-free survival on follow-up [2.1].

2.5. Poorly differentiated carcinoma

Insular carcinoma is the term proposed by Carcangiu, et al. for a distinctive form of poorly differentiated carcinoma arising from follicular cells, characterized by well defined islands or 'insulae' of uniform small cells with round nuclei and scanty cytoplasm. It is an aggressive neoplasm associated with regional and distant metastases and a high mortality rate [2.13]. The prognosis is worse than well differentiated follicular carcinoma and better than anaplastic carcinoma.

Undifferentiated (anaplastic) carcinoma. This is a highly malignant neoplasm that is partly or totally undifferentiated, but shows evidence of epithelial differentiation based on morphologic, immunohistochemical, or ultrastructural grounds [2.1]. Most subjects are elderly individuals with rapidly enlarging thyroid mass. There is a wide spectrum of histologic appearances, but most assume squamoid, spindle cell, and giant cell patterns (Fig. 2.6) with a high degree of invasiveness that can be deduced from high mitotic activity, frequent extrathyroid infiltration, extensive necrosis, and vascular invasion. The outlook remains grim. Neither extent of operation nor completeness of resection has affected survival, and multimodal therapy (surgery, chemotherapy, and radiotherapy) has not improved the high mortality rate [2.14, 2.15].

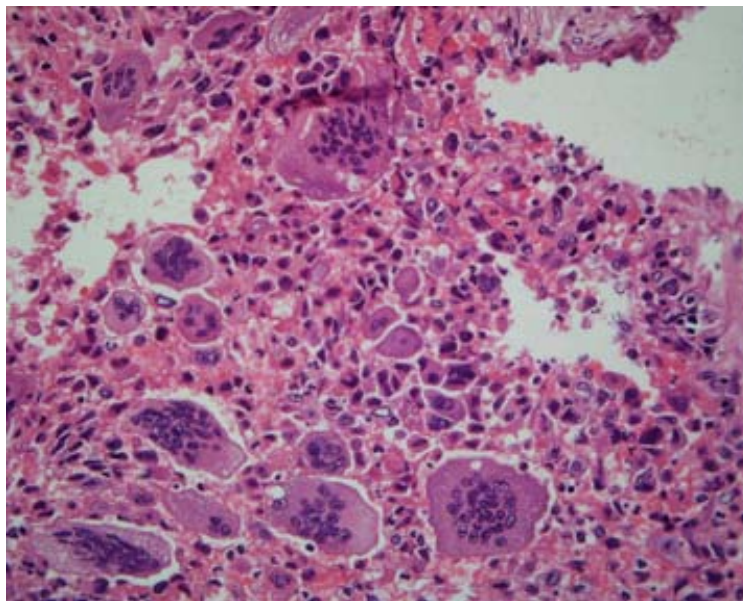


FIG. 2.6. Anaplastic carcinoma. Marked pleomorphism associated with hemorrhage, necrosis, and osteoclast-like multinucleated giant cells scattered among the neoplastic cells.

2.6. Tumours of parafollicular or C cells

Medullary carcinoma is a malignant tumour that arises from parafollicular C cells, which have a neuroendocrine function, responsible for the production of the peptide hormone calcitonin (CT). Measurement of CT levels can therefore aid in the diagnosis and follow up of treatment results. It occurs in sporadic (70%) or familial forms [2.3], and makes up 5-10% of all thyroid cancers. The familial tumours are associated with multiple endocrine neoplasia (MEN) 2A and MEN 2B. It is interesting to note that patients with familial medullary

carcinoma diagnosed by screening (genetic and/or biochemical) and treated early, had a lower incidence of cervical lymph node metastasis and nearly a 100% cure rate [2.16]. Early detection not only of hereditary but even of sporadic medullary thyroid carcinoma by means of calcitonin screening programs permits curative surgery in majority of patients [2.17].

The histology of medullary carcinoma is variable. Architectural patterns include trabecular, follicular, tubular, and cell nests with carcinoid appearance. The tumour cells likewise show morphologic variability — they may appear round or ovoid with peripherally displaced nuclei, spindly, oxyphilic, or anaplastic. One prominent feature is deposition of amyloid in the stroma. (Fig. 2.7). Because it can assume the appearance of other follicular tumours of the thyroid gland, a definitive diagnosis is usually possible only after immunohistochemical staining for endocrine markers, such as calcitonin, chromogranin, synaptophysin, and neuron specific enolase (NSE).

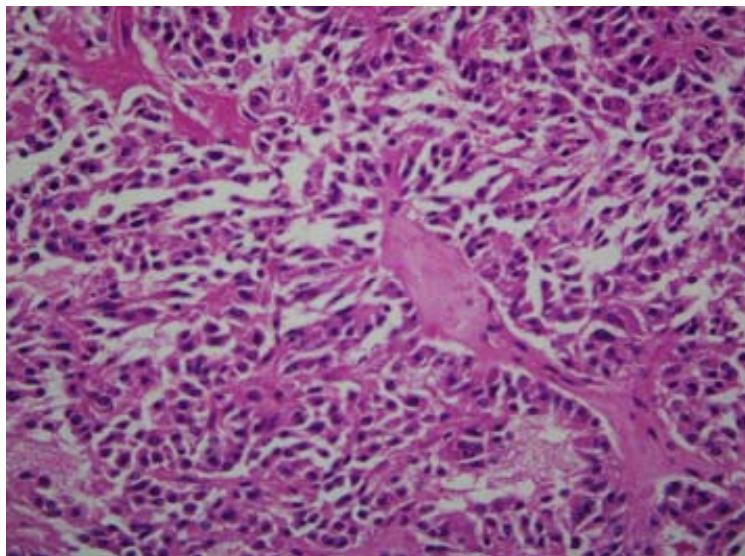


FIG. 2.7. Medullary carcinoma. The tumour is composed of spindly cells with moderate amount of eosinophilic cytoplasm, some assuming plasmacytoid appearance. Focal deposits of amyloid are seen in upper left corner.

Prognosis of medullary carcinoma is related to the following pathologic features: tumour pattern, necrosis, presence of amyloid [2.18], mitotic activity, and aneuploidy.

2.7. Non-epithelial tumours

Malignant lymphoma. Malignant lymphoma of the thyroid gland may occur as part of a systemic lymphoma, or may arise as a primary non-epithelial neoplasm. The latter usually arises in an immunologically altered thyroid gland. In a recent clinicopathologic study of 108 cases, the majority of primary thyroid lymphomas showed features of lymphomas of MALT type, arising in a setting of lymphocytic thyroiditis [2.19]. It is estimated that the risk of malignant lymphoma developing in a patient with lymphocytic thyroiditis is 40-80 times greater than in the general population. Most of the lymphomas are of the diffuse large B-cell type. Clinical stage and histology are the most important prognostic factors — tumours with large cell component or stage greater than 1E being associated with a poor outcome [2.19].

2.8. Summary

The morphologic features of the different types of thyroid cancer have been reviewed, including prognostic factors and recent advances in ancillary procedures which aid in a more precise histological typing. Continuing studies will undoubtedly contribute to more precise diagnosis, earlier treatment with improved cure rates, and even prevention of occurrence of certain thyroid malignancies, particularly those associated with genetic factors in their pathogenesis.

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3. CLINICAL PRESENTATION

3.1. Introduction

The clinical presentation of thyroid cancer is a spectrum. The most common presentation is the incidental, asymptomatic, small, solitary nodule, in which the exclusion of cancer is the major concern. The management of such a solitary thyroid nodule (STN) (Figs 3.1(a)-(b)) is highly controversial [3.1-3.3]. Regional metastatic lymphadenopathy in the neck is rare in adults but is fairly common among children. Rarely, it may present as a large mass, partly retrosternal nodule that causes pressure symptoms or it may present as hoarseness of voice due to infiltration or compression of recurrent laryngeal nerve. In such situation the diagnosis is very obvious.

The prevalence of thyroid nodule varies from country to country, and more so depends on the environmental iodine status. In the United States, which is an iodine sufficient environment, 4 to 7 per cent of the adult population has a palpable thyroid nodule [3.4]. However, only 1 of 20 clinically identified nodules is malignant. This corresponds to approximately 2 to 4 per 100 000 people per year, constituting only 1 per cent of all cancers and 0.5 per cent of all cancer deaths [3.5]. Nodules are more common in women and increase in frequency with age. The prevalence is much greater with the inclusion of nodules that are detected by ultrasonography or at autopsy. By the latter assessment, approximately 50 per cent of 60-year-old persons have thyroid nodules [3.1]. The natural history of solitary thyroid nodules is poorly understood, mainly because nodules that are suspicious for cancer, cause pressure, or produces cosmetic problems are rarely left untreated. With this reservation, it seems that the majority of benign non-functioning nodules also grow, particularly those that are solid [3.6-3.8]. In one study, 89 per cent of nodules that were followed for five years increased by 15 per cent or more in volume [3.8].

The most common diagnoses are colloid nodules, cysts, and thyroiditis approximately in 80 per cent of cases; follicular neoplasms in 10 to 15 per cent; and thyroid carcinoma in 5 per cent. The solitary thyroid nodule that is detected on physical examination, regardless of the finding of additional nodules by radionuclide scanning or ultrasonography has equal probability of malignancy, since such a finding does not alter the risk of cancer [3.1]. The risk of thyroid cancer seems nearly as high in incidental nodules (<10 mm), the majority of which escape detection by palpation, as in larger nodules [3.9]. However, the vast majorities of these microcarcinomas do not grow during long term follow-up and do not cause clinically significant thyroid cancer [3.10].

3.2. History and physical examination

The history and physical examination remain the diagnostic cornerstones in evaluating the patient with a thyroid nodule and may be suggestive of thyroid carcinoma. A high index of clinical suspicion is contemplated when the following clinical features are present in an individual with euthyroid STN: rapidly growing hard or fixed nodule, with palpable neck nodes in central or lateral cervical compartments, with hoarseness of voice, or family history of thyroid cancer, or exposure of head and neck to radiation in childhood. However, a very few of patients with malignant nodules have suggestive findings, which often also occur in patients with benign thyroid disorders. There is also substantial variation among practitioners in evaluating nodules [3.5, 3.11], a finding that may explain why an increasing number of thyroid specialists use imaging as part of the evaluation [3.2, 3.3]. The fact that ultrasonography detects nodules a third of which are more than 20 mm in diameter in up to 50

per cent of patients with a normal neck examination underscores the low specificity and sensitivity of clinical examination [3.12]. When two or more risk factors that indicate a high clinical suspicion are present, the likelihood of cancer approaches 100 per cent [3.13]. In such cases, biopsy is still useful to guide the type of surgery [3.4, 3.5].

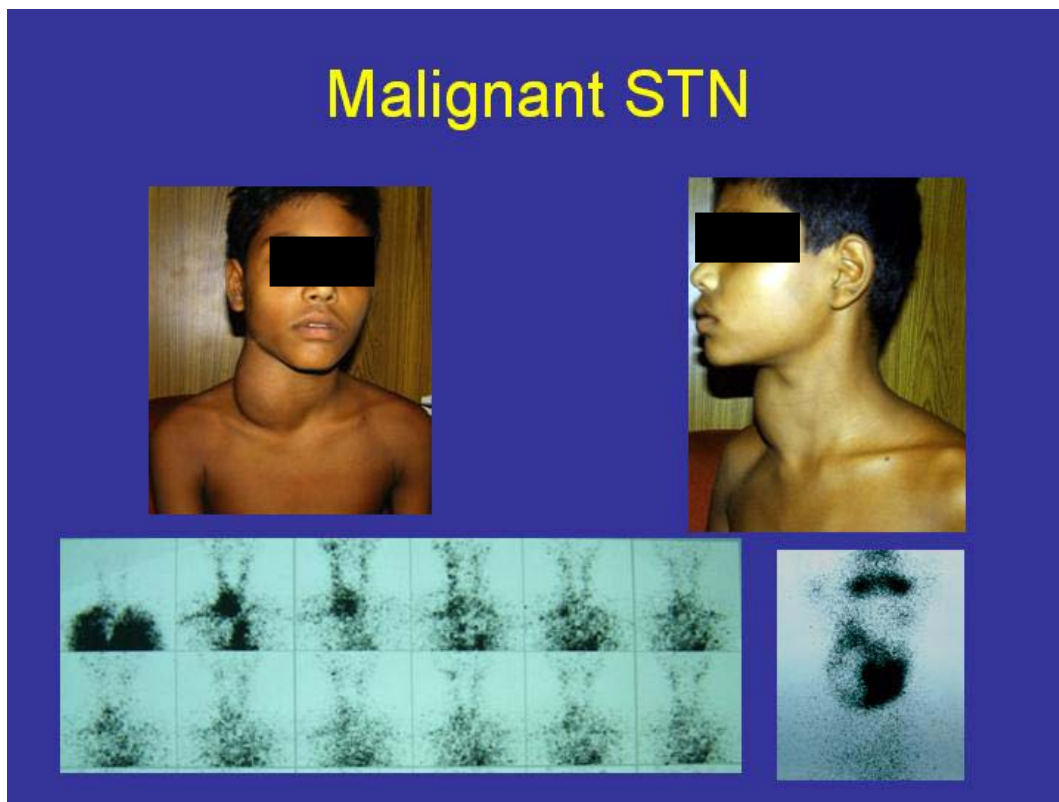


FIG. 3.1. (a) Showing artistic view of STN and clinical photograph of patient with STN, respectively; (b — lower panel) also shows the 370MBq (10 mCi) pertechnetate dynamic and static images of thyroid. A solitary thyroid nodule that washes out quickly and becomes 'cold' in 20-min image, highly suggestive of malignancy. FNA cytology proved this nodule to be papillary carcinoma thyroid.

Intrathyroid papillary carcinomas and microangiopathic follicular carcinomas are very slow growing tumours in patients under the age of forty. This applies also to metastases, which may not be clinically apparent until five to ten or more years after initial thyroidectomy. Such metastases tend to occur either in the lymph nodes (papillary) or in bones (follicular). After the age of forty years, previously diagnosed and newly diagnosed tumours show a tendency to grow and spread more rapidly, usually associated with less well-differentiated histopathology. Lymph node involvement is relatively rare in adults but common in children.

Hurthle cell carcinoma, which is considered to be a variant of follicular cancer presents as bulky and invasive tumour and behave fairly aggressive manner, metastasize widely and prove lethal in a high proportion of patients. They also present as solitary nodules predominantly in the 6th decade of life and with sizes over 4 cm.

Medullary thyroid carcinomas accounts for 5-9% of thyroid neoplasms. Eighty per cent are sporadic and 20% are familial. The familial variety has endocrine abnormalities. MEN-2B has a marfanoid appearance with mucosal neuromatosis and pheochromocytoma while MEN-2A has pheochromocytoma and hyperparathyroidism. The course is variable and the tumour tends to be slowly progressive metastasizing early to the cervical lymph nodes. The sporadic type is commonly unilateral, occurs early in life and is rapidly progressive in type 2B disease. The

familial type is almost always bilateral and may present as a nodule in the 5th and 6th decades. Fifty per cent on presentation are localized and 10% as distant spread and 10% with pressure symptoms. Facial flushing, diarrhoea and elevated calcitonin levels are typical features of the disease.

Anaplastic carcinoma accounts for 1-2% of thyroid cancer and present as a history of recent, very rapid enlargement of a normal or goitrous thyroid gland, with local pressure symptoms, particularly difficulty in breathing. On examination, the thyroid is asymmetrically enlarged or with a large hard mass that is fixed to the underlying structures. Vocal cord paralysis may be present. Frequently, there is a history of a pre-existing goitre and a history of long standing thyroid enlargement in about 80% of patients. There may also be a previous history of well-differentiated thyroid cancer with sudden fulminant disease. It is highly fatal and spreads locally involving the trachea, oesophagus and superior mediastinum by direct extension.

This is the most aggressive form of thyroid cancer and affects the older age group usually over 70 years old. They may present with dysphagia, a painful neck mass or as a superior vena caval syndrome. There is usually a rapid clinical deterioration.

This may also be the picture of the other undifferentiated thyroid carcinomas as in lymphomas, squamous carcinomas, giant and small cell carcinomas, sarcomas and mucoepidermoid carcinoma of the thyroid.

3.3. On clinical examination

Findings in the neck:

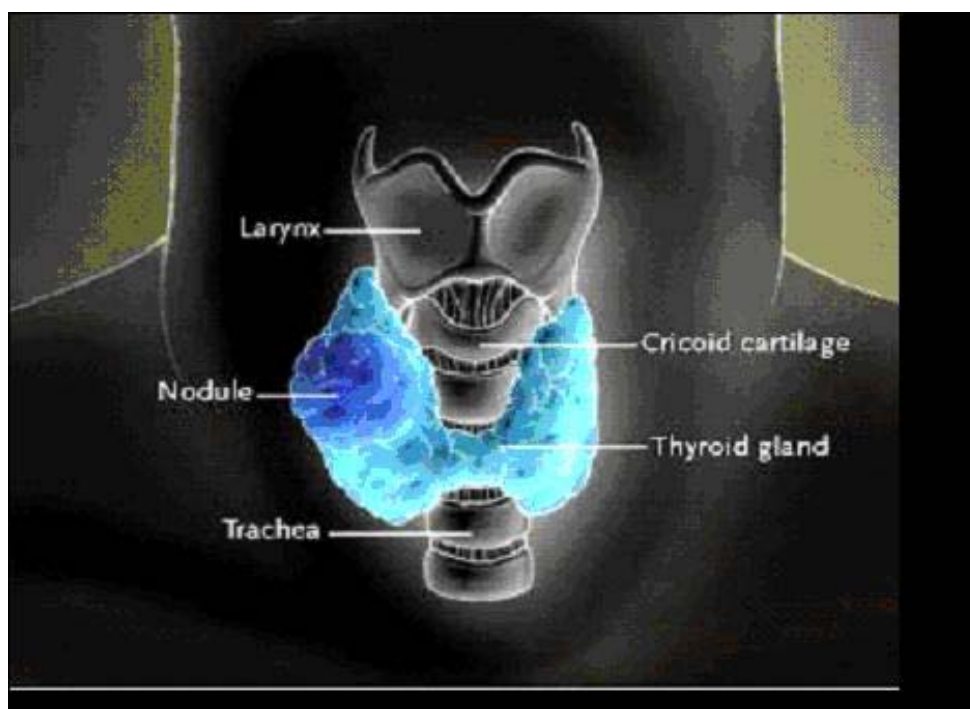


FIG. 3.2. Location of thyroid gland.

Thyroid nodule (Fig. 3.2): The most common presentation of thyroid cancer is a solitary thyroid nodule. It is usually painless though pain may occur if there is haemorrhage in the nodule but is rare. Pain may be the presenting feature of anaplastic thyroid cancer when there is rapid growth of the nodule over weeks that stretch the capsule causing pain or there is

invasion into the skin. The patient may have noticed it incidentally or someone else may have pointed out a swelling in the neck. The swelling may be slowly growing over months or years or rapidly growing over weeks. The general approach to the diagnosis of a solitary thyroid nodule is described in later section and will not be repeated here.

Thyroid cancer, usually of the follicular variety may arise in a long standing multi-nodular goitre. In such cases, patient may present with a dominant nodule in a multinodular goitre (MNG) increasing in size recently.

A patient with recurrence of disease following treatment may also complain of swelling in the neck in the thyroid bed.

Lymph node enlargement: Although microscopic metastasis can be found in up to 50% of cases, palpable lymph node enlargement is much less common though of extreme clinical significance from the points of view of staging and treatment. Nodes in the anterior triangle are more clinically significant than those in the posterior triangle. Patients may present with nodal recurrence.

3.3.1. Findings due to loco-regional spread

Invasion in the surrounding structures, which is recurrent laryngeal nerve, trachea, strap muscles of the neck, or oesophagus, may occur. The patient may present with hoarseness of voice, difficulty in breathing or stridor, or dysphagia.

Superior Vena Cava Syndrome may arise due to spread along the blood vessels in follicular cancer or due to external compression in the case of anaplastic cancer.

3.3.2. Findings due to distant metastasis

Lung Metastasis: Due to the slow growth of thyroid cancer, lung metastasis may be asymptomatic and diagnosed on ^{131}I whole body scan, post therapy scan, chest X ray or CT scan of the thorax (Table 1.1) However, it may cause breathlessness if there is massive replacement of the lung parenchyma or there is concomitant pulmonary disease.

Bone metastasis: Thyroid cancer may spread to appendicular skeleton, skull including base of skull, spine or pelvis. The patient may present with a swelling or a pathological fracture in the case of appendicular skeleton metastasis. In a patient with a pathological fracture of the humerus or femur with an unknown cause, thyroid gland must be carefully examined. Skull metastasis may present as a swelling in the head. A patient may present with diplopia, proptosis or difficulty in swallowing due to base of skull metastasis. Spinal metastasis presents with backache, features of spinal cord compression such as paraparesis/paraplegia, neurogenic bladder or may be incidentally detected on the diagnostic ^{131}I WBS or the post therapy scan. MRI of spine is indicated in these patients particularly in those who are symptomatic. Widespread skeletal metastasis can be extremely painful needing significant attention to pain palliation therapy.

Brain Metastasis: Though rare, a patient with brain metastasis from thyroid cancer may present with or develop features of raised intracranial tension that is, persistent headache, early morning vomiting, diplopia and papilloedema [3.14]. There may be gradually developing motor weakness due to a space occupying lesion. This has implications for further therapy of the patient including radioiodine therapy with respect to dose of radioiodine as well as

management of raised intracranial tension (ICT) with steroids and mannitol during radioiodine therapy. Also, in a patient with brain metastasis from an unknown primary, thyroid gland must be carefully examined as it makes the disease potentially treatable. One should remember small intracranial metastases may not have any clinical feature. A high index of clinical suspicion is required to identify brain metastasis in a known case of thyroid cancer.

Metastasis to other sites: Liver, adrenals, kidneys, skin, etc. are extremely rare. They normally accompanied with other widespread metastatic diseases.

TABLE 3.1. EXTENT OF METASTASES AT THE TIME OF INITIAL PRESENTATION

Country	Localized in thyroid bed	Cervical Lymph Nodes	Distant Metastases	Author
United States		42%	2%	Mazzaferri [3.15]
		35%	6%	Samaan [3.16]
		34%	7.5%	De Groot [3.17]
Canada	42%	12%	19%	Simpson [3.18]
Finland		42%	14%	Fransilla [3.19]
Japan	61%	39%		Ezaki [3.20]
India	4.5%	41.1%	18.8%	Samuel [3.21]
		44%	15.6%	Bal [3.22]
Philippines	44%	39%	17%	Ogbac [3.23]

3.3.3. *Iatrogenic features*

Complications due to surgery: Patients may complain of generalized body aches, tetany, and paraesthesias due to hypocalcemia resulting from hypoparathyroidism. This should be kept in mind while admitting the patients for ¹³¹I therapy and they must be advised to continue taking their calcium supplements while in hospital. There may be hoarseness of voice due to injury to the recurrent laryngeal nerve during the surgery.

Complications due to radioiodine: A patient may complain of pain and redness in the neck due to radiation thyroiditis while in the hospital or after discharge. Radiation sialadenitis may present with pain and swelling in the parotids or other salivary glands and altered taste sensation.

3.3.4. *Others*

Endocrine manifestations:

Hyperthyroidism: Patients with widespread follicular thyroid cancer may secrete excessive amounts of thyroid hormone leading to a thyrotoxic state. Rarely, thyroid cancer may arise in a gland with concomitant Graves' disease. Still rarer is the occurrence of thyrotoxicosis due to malignant thyroiditis caused by invasion of the thyroid follicles by a rapidly growing anaplastic thyroid cancer.

Persistent diarrhoea: Rarely, patients of medullary thyroid cancer may complain of persistent diarrhoea due to excessive secretion of calcitonin, 5-hydroxytryptamine, histamine, prostaglandins, CEA, VIP etc. by the tumour.

Pheochromocytoma and Hyperparathyroidism: Patients of Medullary thyroid cancer with MEN IIa and IIb may have clinical features of pheochromocytoma and patients with MEN IIa may also have features of hyperparathyroidism.

3.3.5. *Past history*

A past history of irradiation to the head and neck during childhood maybe present in some patients of thyroid cancer. A history of concomitant illnesses such as hypertension, diabetes, etc. should be noted to aid in the in-patient management of the patient (Fig. 3.3).

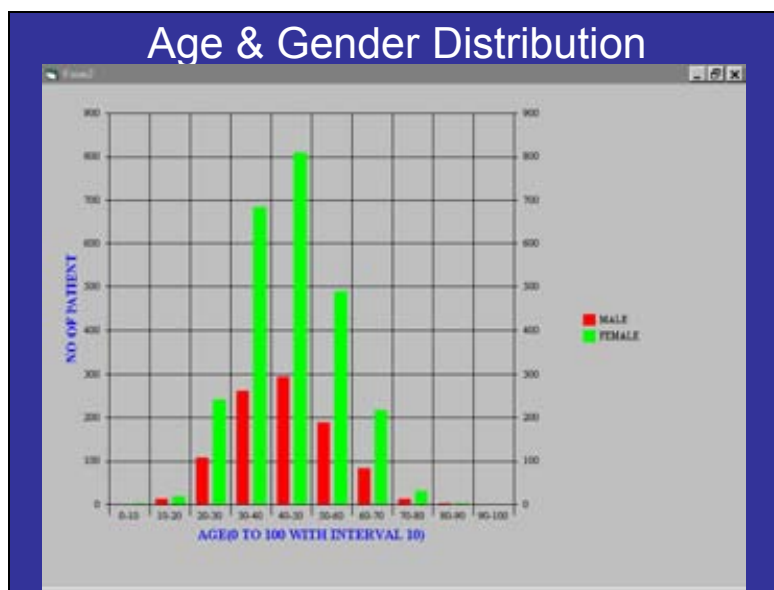


FIG. 3.3. Distribution of age and sex in this series of 2400 patients from India [3.22].

3.3.6. *Family history*

Familial medullary thyroid cancer may present as MEN IIa, MEN IIb and familial non-MEN medullary carcinoma thyroid, all of which are autosomal dominant conditions.

Summarizing the clinical presentation, a large percentage is asymptomatic, and a small number of those with differentiated cancers of the thyroid present with signs of metastases in the form of dysphagia, hoarseness, breathlessness, pathological fractures, bone pains or CNS manifestations. A large portion of differentiated thyroid cancer is papillary and involves the female population affecting those who are at the third and fourth decade of life. The most common presentation is a solitary nodule and the presence and extent of metastases vary from one country to another. Intrathyroidal disease is more prevalent in the middle age group while metastatic disease is prevalent in the extremes of ages. This is corroborated by published literatures. Nodal disease as well as pulmonary is common in children while skeletal metastases are common in the elderly.

3.4. Conclusion

For the patient who presents with a nodule, the main concern is to exclude the possibility of thyroid cancer, even though the vast majority of nodules are benign. The initial evaluation should include measurement of the serum thyrotropin level and a fine-needle aspiration, preferably guided by ultrasonography. If the patient has a family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, the serum calcitonin level should also be checked. If the thyrotropin level is suppressed, radionuclide scanning should be performed. In patients less than 20 years old and in the case of a high clinical suspicion for cancer (e.g., follicular neoplasia as diagnosed by fine-needle aspiration and a non-functioning nodule revealed on scanning), the patient should be offered hemithyroidectomy regardless of the results of fine-needle aspiration.

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4. THYROGLOBULIN

Thyroglobulin is a large (660 kd) homodimeric glycoprotein molecule, encoded by a gene on chromosome 8 that is secreted uniquely by thyroid follicular cells [4.1]. The factors controlling Tg gene expression include thyrotropin (TSH), insulin and insulin-like growth factor-I (IGF-I), which act synergistically to stimulate transcription of the 8.5 kilobase (kb) Tg mRNA, whereas epidermal growth factor (EGF), interferon- γ , tumour necrosis factor (TNF- α), and retinoic acid are inhibitors of transcription [4.2-4.8]. Thyroglobulin is synthesized in the endoplasmic reticulum, modified in the golgi apparatus, and transported to the colloid for storage. The formation of mature Tg requires complex processing that involves dimerization and folding, glycosylation and modification, followed by incorporation into exocytotic vesicles for export into the lumen of thyroid follicles, after which thyroid peroxidase catalyses iodination of tyrosyl residues. (Tg gets iodinated at the apical membrane of the cell where a conformational change takes place depending upon the iodine content) and coupling of some of them within the Tg polypeptide to form thyroxine (T₄) and triiodothyronine (T₃) [4.9-4.12]. Synthesis and secretion of Tg is regulated by TSH as is evident from studies in humans where exogenous injection of TSH or endogenously raised TSH after administration of thyrotropin releasing hormone results in a rise in serum Tg level. Moreover, the administration of thyroid hormones results in lowering of Tg levels with a concomitant fall in TSH level.

Thyroglobulin in thyroid tissue and serum is heterogeneous [4.13]. All the steps involved in post-translational processing can affect the ultimate conformation and immunoreactivity of Tg. Antibodies used in Tg immunoassays are conformational, that is, directed against discontinuous regions of the protein [4.14]. Conformational differences in Tg arising from differences in its composition of carbohydrate [4.15, 4.16] or iodine [4.17, 4.18] can expose or mask epitopes [4.19] and cause antibody-dependent differences in immunoactivity [4.20, 4.21]. Some monoclonal antibodies detect differences between the Tg isoforms present in the glandular extracts used for assay standardization as compared with Tg isoforms in the circulation [4.20]. This can have clinical consequences when using serum Tg as a marker for thyroid carcinomas that secrete conformationally abnormal Tg molecules [4.19, 4.20, 4.22].

The processes involved in the release of Tg into and clearance from the circulation are poorly understood. Tg in the follicular lumen is internalized by micropinocytosis and undergoes proteolytic cleavage in lysosomes, a process that liberates T₄ and T₃ while degrading 90% or more of the Tg molecules [4.23-4.25]. Undigested Tg enters the circulation via thyrolymphatic system by a poorly understood mechanism, either because lysosomal hydrolysis is incomplete or as a result of short-loop secretion that does not involve luminal storage [4.26]. The latter may represent the major route of secretion by thyroid carcinomas in which both glandular and circulating forms of Tg are poorly iodinated.

During steady-state conditions, the serum Tg concentration is determined by the balance between its secretion and metabolism. The mechanisms for clearing Tg from the circulation are poorly understood, but they are thought to be influenced by the sialic acid content of the molecule; its presence appears to facilitate clearance. Hepatocytes are thought to mediate most extrathyroidal Tg metabolism; Tg binds to B-lymphocytes and other cells, but the metabolic importance of this binding is unclear. In normal subjects the secretion rate and plasma half-life of Tg are 100 mg/60 kg/day and 29.6 \pm 2.8 hours, respectively. In general, 1 g of normal thyroid tissue results in a serum Tg of approximately 1 μ g/litre when the TSH is in the normal range and about 0.5 μ g/litre when TSH is suppressed [4.27]. The half-life after thyroidectomy is shorter in patients with Graves' disease or differentiated thyroid carcinoma and longer in patients with nodular goitre. The different Tg half-life estimates, ranging from

2.5 hours to 6 days may be due to variations in clearance resulting from release of Tg molecules of different size or sialic acid content [4.16]. In addition, there may be differences in immunoreactivity between the exogenously administered Tg preparations used for some clearance studies as compared with endogenous Tg measured in the post-thyroidectomy studies. In the case of Graves' disease, it is postulated that formation of Tg-TgAb complexes might increase Tg clearance.

4.1. Serum thyroglobulin measurements and its limitations

Tg was considered a secluded antigen present within the thyroid epithelial cells and not a naturally circulating protein and hence its presence in serum was believed to evoke an immune response and cause production of autoantibodies. However, with the demonstration of inhibition of haemagglutination by a serum from pregnant women, Tg was established to be a normal component of serum. Later electrophoresis confirmed the presence of Tg like material in the sera of normal subjects. Radioiodinated Tg was reported in the sera of patients of differentiated thyroid carcinoma (DTC) treated with radioiodine (^{131}I). The development of radioimmunoassay (RIA) for measurement of serum in monkeys and in humans soon followed.

Several methods for measurement of serum Tg, such as RIA, Immunoradiometric assay (IRMA), [4.28], Enzyme Link Immuno Sorbant Assay (ELISA) [4.29] and other IMAs with nonisotopic labels [4.30] are currently being used depending upon the requirement and available facilities at the institution. Radioimmunoassay is the most widely used system, however, in recent years the IMAs have gained popularity because of (a) shorter incubation periods, (b) wider working range, (c) more stable labelled antibody preparations and (d) shorter reporting time. Assays using non-isotopic labels with high sensitivity and precision have also been developed. A wide variation has been observed in the assay characteristics reported by several laboratories. The technical details of the methodology used for serum Tg determination along with the clinical status of the patient is extremely important for a meaningful interpretation of serum Tg results. The following factors play a crucial role in Tg estimation:

4.1.1. Variability of reagents

Since there is a lack of availability of an international standard Tg preparation the source of the antigen used may differ amongst laboratories. Thyroglobulin is a very large molecule and has several antigenic determinants and many isoforms. Biochemical variations in the Tg molecule in terms of amino acid composition, carbohydrate content and iodide content have been demonstrated [4.31]. A differential splicing of Tg mRNA [4.16, 4.18] may also confer differences in antigenicity and result in wider interlaboratory variations. Efforts are being made to standardize an international preparation and recently a standard Tg preparation (CR 457) has been produced as a result of efforts by commission for European communities. Although this has improved intermethod variation, differences between methods still exist [4.32].

Another source of variation amongst Tg preparations is the inherent instability of the Tg molecule due to its high susceptibility to proteolysis. Even under ideal conditions of storage (using protease inhibitors, storing at -40°C , making several aliquots for preventing frequent freezing and thawing, preparing stocks in carrier protein, etc.), it tends to degrade. The altered antigenic properties of degraded Tg may result in under or, over estimation of serum Tg. Even amongst the commercial kits available, there are variations due to differences in reagents.

Serum thyroglobulin is a heterogeneous population [4.16, 4.18, 4.19, 4.21, 4.31] and immunological differences among circulating Tg and that derived from thyroid tissue have been described. The antibodies used in the immunoassay are directed towards epitope located in the discontinuous region and therefore recognize conformational isoforms of Tg [4.14]. The use of highly specific monoclonal antibodies for measurement of serum Tg by several investigators have shown that abnormal isoforms of Tg secreted by tumour may remain undetected in such systems [4.18, 4.19, 4.22]. Therefore the antisera used by different laboratories may also explain variable inter-laboratory results.

4.1.2. Hook effect

The Hook effect results from a large amount of the antigen, which saturates the binding and gives a falsely negative value and is applicable to one step solid phase sandwich assays. Though such sera are relatively few, it is important to identify them so that the assay can be performed at various dilutions of sera.

4.1.3. Interference from thyroglobulin autoantibodies

TgAb interference affects all Tg methods to some degree by causing over or underestimation of serum Tg concentrations [4.33]. With RIA methods the direction of interference depends on the method used to separate antibody-bound and free Tg, the volume of serum used, and the concentration and affinity of the serum TgAb, because these factors affect the partitioning of Tg tracer between the antibody constituents. Underestimation is the characteristic pattern of interference in immunometric assays because Tg complexed with TgAb appears to be blocked from participating in the two-site reaction.

Some normal subjects have low serum TgAb concentrations [4.36], whereas high serum TgAb concentrations are characteristic of autoimmune thyroid disorders [4.37]. It is unclear whether very low concentrations of naturally occurring TgAb are the cause of the interference found with some seemingly TgAb-negative serum samples [4.38]. Epitope mapping of Tg reveals six different antigenic domains (regions I-VI) with different specificity for naturally occurring TgAb [4.39, 4.40]. Most laboratories still use insensitive hemagglutination techniques to detect TgAb in serum despite reports that TgAb concentrations too low to be detected by hemagglutination can interfere with serum Tg measurements [4.41]. Sensitive TgAb immunoassay methods are recommended for screening serum for interfering TgAb before Tg measurement is undertaken. Using immunoassays, TgAb can be detected in 4% to 27% of normal subjects, 20% to 45% of patients with thyroid carcinoma [4.42-4.43], and 50% to 97% of patients with autoimmune thyroid disease [4.44]. It is difficult to predict which serum samples with TgAb will interfere with serum Tg measurements because the TgAb concentration does not correlate with the degree of interference assessed by recovery or dilution studies [4.34, 4.38]. Attempts to overcome TgAb interference in immunometric assay by using monoclonal antibodies restricted to epitopes not involved in autoantibody formation has not overcome the interference problem [4.34], either because the in vitro recovery approach is invalid or because the TgAb in patients with thyroid carcinoma reacts with more epitopes than TgAb in patients with autoimmune thyroid disease [4.35]. Thus, any serum Tg value reported in patients with TgAb must be interpreted cautiously. In fact, it is probably better not to report serum Tg values at all in patients with TgAb in their serum, unless the Tg assay method can be shown to give serum Tg values concordant with clinical status.

4.1.4. Critical level for discerning the disease

The range or the cut-off value used in different clinical conditions to ascertain the recurrence, presence or absence of disease is most important. Theoretically, it should be derived from non-cancerous athyrotic individuals (patients or controls). However, it is practically impossible and not ethical to have such a situation. Alternatively, it is derived from patients of DTC who are adequately treated with surgery and ^{131}I and have no detectable remnant neck tissue or metastases by clinical, radiological or any of the imaging modalities. At least a minimum disease free period of 5 year after adequate treatment is required for establishing the cut-off value. The cut-off value is then derived as 95 percentile value. Error in any of the above criteria may result in an inappropriate critical level.

4.2. Normal serum thyroglobulin concentrations

In embryonic stage, the thyroid gland differentiates and Tg gene expression is initiated in the absence of TSH, before thyrotrophs are detected. TSH and thyroid hormones synthesis begin near mid gestation in human; thereafter, the pituitary-thyroid axis matures with the development of thyroid hormone feedback inhibition of TSH during the third trimester [4.45]. At birth the serum concentrations of T_4 , free T_4 , and T_3 are correlated positively, whereas serum Tg and TSH concentration are correlated negatively with gestational age and birth weight. Cord serum Tg and TSH concentrations are correlated positively [4.46] and are higher than maternal concentration [4.45]. Although the fetal and maternal thyroid axis are controlled independently, maternal iodine intake influences fetal thyroid function such that cord serum Tg concentrations are correlated negatively with maternal urinary iodine excretion at the time of delivery [4.46]. The high cord serum Tg values typical of iodide-deficient areas presumably reflect either higher serum TSH concentrations [4.46], enhanced secretion of poorly iodinated Tg, or decreased clearance of Tg by the immature new born liver. Thyroid size and cord serum Tg concentrations are increased in infants born to smoking mothers [4.47]. This is thought to be secondary to a goiterogenic effect of thyocyanite, the concentrations of which are correlated positively in cord and maternal serum [4.48].

Although, infants with congenital hypothyroidism usually have abnormally low or high serum Tg concentration depending on the underlying pathology, the serum Tg concentration is not diagnostic [4.49]. The Tg value together with the results of ultrasonography and radionuclide imaging of the thyroid can be used to determine the aetiology of congenital hypothyroidism [4.50]. Low but detectable serum Tg concentrations are characteristic of both thyroid agenesis and thyroid ectopy [4.50, 4.51]. Serum Tg concentrations are high, sometimes very high (1000 ng/ml), in infants with thyroid hormone resistance, iodide transport or deiodinase defects and other inborn errors of T_4 biosynthesis [4.50, 4.52, 4.53]. In normal full term infants serum Tg increases in the first days after birth presumably in response to the post-natal surge in TSH secretion; this increase is attenuated in sick or pre-term neonates. Serum Tg concentrations fall approximately 50% during the first few months of life, after which they decline very gradually to reach adult level after puberty.

Thyroglobulin can be detected in the serum of all normal subjects when sensitive methods are used [4.35]. There is no diurnal or seasonal variability in serum Tg concentrations, but the concentration does appear to be under the control of a dominant gene [4.54, 4.55]. The long term intraperson biologic variation is relatively small, whereas interperson variability is high.

Three factors determine serum Tg concentrations in most clinical situations: thyroid cell mass [4.56, 4.57]; physical damage to the thyroid caused by biopsy [4.58], surgery [4.59, 4.60],

hemorrhage, radioiodine administration, external irradiation [4.61], or inflammation; and activation of TSH-receptors by either TSH [4.2], chorionic gonadotropin (hCG) [4.62] or thyroid stimulating antibodies (TSAb) [4.63]. At steady state, thyroid size is the dominant factor, modulating serum Tg concentrations [4.56, 4.57]. Serum TSH and Tg concentrations are correlated only in patients with endemic goitre who have elevated serum TSH concentrations. However, serum Tg changes in parallel with serum TSH when thyroid size remains constant; for example, serum Tg declines with serum TSH during fasting and rises in response to iodine induced or hypothyroidism induced increases in serum TSH [4.64].

Serum Tg levels are significantly higher in women on oestrogen therapy as compared to those in the control group which explains the raised Tg level in women. However, increase in serum Tg in advanced age where the oestrogen levels would be low argues against the role of oestrogen alone as the factor responsible for raised Tg level in women. Age also does not seem to affect serum Tg level [4.58]. These findings are suggestive of the involvement of other factors. Serum Tg concentrations change in parallel with the small changes in thyroid size that occur during the menstrual cycle and are higher in pregnant women than in non-pregnant women; specially during the third trimester [4.56, 4.57]. At delivery serum Tg is correlated with both thyroid size as assessed by ultrasonography and serum TSH [4.57]. Factors responsible for the rise in serum Tg concentrations during pregnancy include hCG (early in pregnancy) and TSH (later) [4.62]. Mild hypertriglyceridemia is also known to cause an increase in Tg level [4.65].

4.3. Role of thyroglobulin in thyroid cancer

4.3.1. *In primary diagnosis*

Although Tg is present in most differentiated thyroid carcinomas and some anaplastic thyroid carcinomas [4.66], the preoperative diagnostic or prognostic value of serum Tg measurement is limited because the concentration may be increased in patients with either benign or malignant thyroid disease and the Tg content of thyroid tumour tissue correlates poorly with serum Tg concentrations [4.67]. Furthermore, a normal serum Tg value does not exclude carcinoma in any patient with thyroid nodular disease. However, immunostaining of tissue for Tg is a useful histological probe for identifying metastases of thyroid carcinoma and for identifying neck masses being of thyroid origin [4.67, 4.68]. Among patients with thyroid carcinoma, serum Tg concentrations are usually higher in those with follicular carcinoma than in those with papillary carcinoma probably because follicular carcinomas are more advanced at the time of diagnosis rather than because of any intrinsic differences between the two tumour types. Among patients with proven differentiated thyroid carcinoma, preoperative serum Tg concentrations are possibly correlated with tumour mass [4.69].

4.3.2. *In post-surgical management*

The difference between pre and postoperative serum Tg values is an indicator of the completeness of the surgery. The relationship between basal and TSH-stimulated serum Tg concentrations may become a useful test for detecting the absence of any thyroid tissue and also providing information on the TSH sensitivity of any thyroid carcinoma tissue [4.43]. A Tg that remains undetectable (<1 µg/litre) after either thyroid hormone withdraw (THW) or recombinant TSH (rhTSH) stimulation is strong evidence of complete tumour ablation in a low-risk patient [4.70-4.78]. Such patients usually require nothing more than annual physical examination and serum Tg measurement during THST, unless there is clinical evidence of tumour or other compelling reasons for performing TSH-stimulated testing. In view of a

positive relationship between Tg and TSH, it has been proposed that the levels of Tg could be used as a biological endpoint for titrating the dose of thyroxin [4.39]. Patients who are athyreotic, as judged by no serum Tg response to TSH, will likely need only T₄ replacement and not suppression therapy. Those with a low basal serum Tg concentration and a minimal response to TSH would probably have only a small amount of thyroid tissue unlikely to be detected by radioiodine imaging. A detectable basal serum Tg concentration but a poor response to TSH would suggest the presence of a poorly differentiated tumour with lower clinical efficacy for TSH suppression therapy. In contrast, a detectable basal serum Tg concentration associated with a substantial response to TSH would suggest the presence of a remnant of normal thyroid tissue or of some well-differentiated carcinoma tissue that will respond to TSH suppression.

4.3.3. In follow-up

Serial determination of serum Tg level is useful for early prediction of recurrence, efficacy of therapy and monitoring the course of the disease in patients with differentiated thyroid carcinoma (DTC) who have been adequately treated with surgery and/or ¹³¹I. It serves as a specific biochemical tumour marker in treated cases of DTC as only tissues of thyroidal origin have the capability of synthesizing Tg. A rise in the level of Tg is indicative of a recurrence or presence of metastases while a fall indicates regression of the tumour [4.79, 4.80]. The levels of Tg are influenced by the presence of remnant tissue in the neck after surgery, the presence and site of metastatic disease, tumour type, and the hormonal status (levels of TSH at the time of measurement of Tg). With the exception of one study [4.81], a good positive correlation between the amount of thyroid tissue and the levels of serum Tg has been observed by several investigators [4.74].

Serum Tg levels are raised in most patients with metastatic disease of DTC. The reported sensitivity for detection of metastatic disease varies between 52-100% while the specificity ranges between 5.9-100%. Occasionally, serum Tg levels are low in spite of the presence of proven metastases [4.82]. In such cases the tumour is either poorly differentiated or the Tg produced by the tumour is structurally altered and not detected in the immunoassay. It is also related to the location of the metastatic site, with higher values in distal metastases [4.83] as compared to regional spread. The sensitivity for detection of osseous metastatic disease (high serum Tg level) has been 100% [4.83, 4.85]. A low serum Tg value does not always rule out the involvement of the thyroid as a primary site of malignancy as some undifferentiated or poorly differentiated tumours and at times nodal diseases fail to show elevated serum Tg in appreciable amounts [4.45, 4.80, 4.82, 4.85, 4.86]. However, it should be emphasized that low levels associated with bone metastasis always rules out thyroidal involvement [4.85].

Since metastatic tissues of follicular thyroid origin synthesize and secrete thyroglobulin, the determination of serum Tg provides a valuable diagnostic test for establishing or ruling out the thyroid as a primary site of tumour in metastatic disease of primary unknown origin. In view of long term survival and availability of a definite therapeutic modality in the form of surgery followed by ¹³¹I, identification of involvement of thyroidal origin is of great value in the management of this disease.

4.4. Comparison during and after withdrawal of thyroid hormone therapy or after rhTSH injection

While there is a general agreement on the measurement of Tg as a reliable marker for follow-up of a patient of DTC, there has been a considerable controversy as to whether it should be

measured while patients are on thyroxin therapy or whether the thyroxin therapy should be suspended for its clinical utility. Some advocate measurement while patients are on thyroxin therapy [4.87, 4.88] while others find it more useful to measure Tg during withdrawal of thyroid hormone therapy [4.82, 4.89, 4.90]. Thyroglobulin levels are usually lower while on thyroxin medication [4.90, 4.91]. In metastatic disease, serum Tg levels are detectable on thyroxin therapy, though the levels are lower than when stimulated.

The consensus is that an undetectable serum Tg measured during thyroid hormone suppression is misleading in a large proportion of patients with residual DTC. An undetectable serum Tg during THST is usually achieved only by total or near-total thyroidectomy and ¹³¹I ablation. For example, one study [4.90] of 180 patients with DTC found that THST-Tg levels were often above 10 µg/litre after partial thyroidectomy, with or without ¹³¹I ablation. Even after near-total or total thyroidectomy and ¹³¹I ablation, Tg levels were higher than 10 µg/litre in almost 2% of patients during THST [4.91]. On the other hand, among patients displaying a low or undetectable serum Tg level during THST, the Tg often rises to above 2 µg/litre after TSH stimulation. In a Phase III rhTSH study [4.72], for example, a serum Tg lower than 2 µg/litre measured during THST failed to identify 23% of evaluable patients with metastatic disease, yet a TSH-stimulated Tg above 2 µg/litre (rhTSH or THW) identified all patients with metastases. In eight studies [4.75-4.77, 4.92] comprising a total of 1028 low-risk patients thought to be clinically free of disease, the Tg level was less than 1 µg/litre during THST in 76% (784 of 1028 patients), rising above 2 µg/litre in 21% (165 of 784 patients) in response to rhTSH. When this occurred, almost 36% (60 of 784) had metastases, of which over 36% (22 of 784) were at distant sites.

Among patients with an undetectable THST-Tg who undergo rhTSH stimulation, there are three possible scenarios using a Tg cut-off of 2 µg/litre:

a) Tg remains undetectable: Up to 65% of low-risk patients who have undergone near-total thyroidectomy and ¹³¹I ablation have no rise in serum Tg concentrations after rhTSH. Annual TSH-stimulated serum Tg measurement does not need to be done in this group, but thereafter how often or whether it should be done at all is uncertain.

b) Tg rises but not higher than 2 µg/litre: This occurs in about 20% of low-risk patients and may not call for immediate evaluation but usually warrants periodic rhTSH stimulation studies, perhaps as often as once yearly. Neck ultrasonography plays an important diagnostic role in this group. In some patients, the high TSH-stimulated serum Tg level will spontaneously decline over one or more years, and in others it will steadily rise, and metastases will become apparent [4.70, 4.90, 4.92].

c) Tg rises above 2 µg/litre: This occurs in about 20% of low-risk patients after rhTSH stimulation and usually indicates a substantial thyroid remnant or residual cancer. Patients with this pattern usually require further testing to localize the source of the Tg.

It appears that hypothyroid and euthyroid rhTSH-stimulated serum Tg levels (measured 72 h after the last dose of rhTSH) are comparable in detecting metastases when a cut-off of 2 µg/litre is used. Considerable evidence supports the notion that the two methods used to stimulate Tg, THW-induced hypothyroidism and euthyroid rhTSH stimulation, are equally effective in detecting metastatic thyroid cancer [JCEM]. In a large phase III rhTSH study [4.72], the median serum Tg values were 0.5 µg/litre during THST, 1.1 µg/litre 72 h after the last of two 0.9 mg doses of rhTSH, and 1.8 µg/litre during THW; however, using a Tg cut-off of 2 µg/litre, all metastases were identified with either an rhTSH- or THW-stimulated Tg test.

Robbins, et al. [4.93] were unable to demonstrate a difference in the diagnostic accuracy of serum Tg concentrations in the detection of metastases among patients prepared by either THW (161 patients) or rhTSH (128 patients). Pacini, et al. [4.76], comparing peak rhTSH- and THW-stimulated serum Tg concentrations in the same patients, found that none of those with a TSH-stimulated Tg less than 1 µg/litre had metastases, whereas an elevated TSH-stimulated Tg identified 100% of the patients with local or distant metastases, regardless of whether the TSH stimulation was by rhTSH or THW. In eight recent studies [4.71-4.77, 4.92], an rhTSH-stimulated Tg above 2 µg/litre identified 91% of the 58 patients with metastases.

4.5. Comparison of thyroglobulin with whole body radioiodine scan

Conventionally, for long term monitoring both serum Tg measurement and frequent radioiodine whole body imaging are used for detecting recurrent thyroid carcinoma [4.94]. Periodic radioiodine imaging is inconvenient and costly, and serum Tg measurements have replaced or at least greatly reduced the need for imaging [4.87]. The combined use of serum Tg measurements and radioiodine imaging increases overall diagnostic sensitivity and specificity over either procedure alone [4.95, 4.96]. The exogenous thyroid hormone therapy must be discontinued before radioiodine imaging. With respect to serum Tg measurements, the sensitivity for detecting thyroid tissue, particularly tumour, is increased after thyroid hormone therapy is discontinued [4.88, 4.90, 4.95-4.97].

While the results obtained by ¹³¹I WBS and serum Tg determinations are well correlated in a majority of the cases, in a few cases there is a disagreement between the two tests. Whether a single determination of serum Tg can replace ¹³¹I WBS has been an issue of controversy in view of the merits and demerits of the two techniques as described earlier. The consensus is that a TSH-stimulated Tg alone is sufficient for follow-up of low-risk patients with no clinical evidence of disease and suppressed serum Tg levels during THST. Although serum Tg and DxWBS have been considered complementary in identifying residual tumour [4.98], an undetectable TSH-stimulated Tg alone, whether by THW or rhTSH, is usually sufficient to do this. Little information is added by performing a DxWBS in the evaluation of patients at low-risk of having persistent disease. Tumour is rarely found when the serum Tg value is less than 2 µg/litre after rhTSH stimulation [4.71-4.77, 4.92] or THW [4.70, 4.78]. Two THW studies showed that TSH-stimulated serum Tg measurement consistently identifies patients with residual tumour [4.70, 4.78]. Eight other studies [4.71-4.77, 4.92] showed that metastatic tumour is almost always identified by an rhTSH-stimulated serum Tg above 2 µg/litre. Six of the eight studies [4.71, 4.73-4.76, 4.92] show the extent to which unsuspected tumour is detected by Recombinant TSH (rhTSH) -Tg and DxWBS. When 784 patients underwent testing, 36% of those with an rhTSH-Tg above 2 µg/litre were found to have unsuspected metastases that were usually not detected by DxWBS. Almost all (91%) of the patients with metastases were identified by an rhTSH-stimulated Tg above 2 µg/litre, whereas only 19% were identified by a positive rhTSH-stimulated or hypothyroid THW DxWBS. Thus, 10 studies [4.70-4.78, 4.92] comprising 1599 patients demonstrate that TSH-stimulated Tg testing (either rhTSH or THW) is sufficiently sensitive to be used alone in the follow-up management of low-risk patients with DTC.

In studies comparing the serum Tg level and WBS to detect the metastatic disease, if present, an overall sensitivity for WBS varied between 50-100% while the corresponding range for serum Tg was 52% to 100% [4.42, 4.80, 4.88, 4.90, 4.95, 4.96, 4.99]. An increased sensitivity for detection of recurrence by serum Tg levels in comparison to WBS has been reported by some [4.82, 4.87, 4.95, 4.100], while other investigators find WBS to be superior to serum Tg

level [4.42, 4.96]. The superiority of serum Tg determination over WBS has perhaps been due to the limitations of detection of small volumes of the tissue by scintiscan as compared to the ability to detect small amount of Tg in serum. However, studies comparing the sensitivity measurements of serum Tg and radioiodine imaging for detecting persistent or recurrent thyroid carcinoma are complicated by differences in TSH secretory status, imaging technique, and disparities between serum Tg assay methods [4.33].

In about 10-15% of the cases the WBS is negative in spite of the presence of metastases as evident from other imaging modalities with elevated serum Tg level. This set of results usually occurs because the radioiodine scan is falsely negative rather than the serum Tg value being falsely positive [4.101]. A negative scan is suggestive of (a) low fractional tumour uptake, (b) a smaller volume of tumour to be detected on scintiscan, (c) increased dietary iodide consumption that results in an increase in the stable iodide pool and decreased ^{131}I uptake, (d) presence of remnant normal thyroid tissue or (e) the tumour has lost the capacity to trap iodide but is capable of synthesizing Tg. In such patients the metastatic disease is detected in up to 90% of cases by high therapeutic doses of ^{131}I [4.89, 4.97, 4.102-4.105]. This blind treatment with ^{131}I not only locates the site of metastases but also delivers a therapeutic dose which is curative at times [4.102, 4.105-4.107] and which is evident by a decrease in the Tg level during follow-up. A negative scan with a high serum Tg level therefore, requires a thorough work-up with therapeutic dose of ^{131}I . An absolute relationship of serum Tg level with ^{131}I uptake may not always be evident as the tumours may synthesize Tg but not necessarily trap iodine and these properties may vary from tumour to tumour.

Discordance characterized by an undetectable serum Tg value and a positive radioiodine scan is infrequent. This discordance may reflect a false-negative serum Tg value due to assay insensitivity, the selection of a high cut-off value, or an underestimation of serum Tg as a result of TgAb interferences [4.34]. A false-negative serum Tg value also can occur if a tumour secretes a conformationally abnormal Tg molecule that is not detected in the Tg assay used [4.20]. The therapeutic dose of ^{131}I in such situations detects the metastases, which more often is localized to the thyroid bed only [4.10].

4.6. Conclusions

Measurement of serum Tg is of limited value in the diagnosis of primary thyroid tumour but is very useful in post-operative management of differentiated thyroid carcinoma. The sensitivity and the specificity of Tg determination is comparable to that obtained with WBS, however, both are complimentary. Hypothyroid and euthyroid rhTSH-stimulated serum Tg levels (measured 72 h after the last dose of rhTSH) are comparable in detecting metastases when a cut-off of 2 $\mu\text{g}/\text{litre}$ is used. Serum Tg measurements during thyroid hormone suppression are sufficiently sensitive to forgo further testing in a low-risk patient who is clinically free of disease and has had an undetectable (<1 $\mu\text{g}/\text{litre}$) serum Tg level during THST and after rhTSH or THW. In patients with metastatic disease of primary unknown origin, high levels of Tg in circulation or demonstration of Tg in metastatic tissue specimen by immunohistochemistry is indicative of involvement of thyroid as a primary organ.

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5. RADIOLOGICAL IMAGING

The thyroid gland can be imaged with multiple modalities viz., nuclear medicine, high resolution US, thin section CT and MRI. However, the initial methods of evaluation of thyroid disease remains clinical history, physical examination, and laboratory values, potentially augmented by palpation-guided fine needle aspiration biopsy (FNAB) [5.1]. The endocrine aspects of thyroid diseases rarely require imaging for diagnosis. However, the non-endocrinal aspects produce many radiological signs and these may influence clinical management.

The thyroid gland is critical in regulating various metabolic functions; thus, patients with hormonally active thyroid gland present with wide-ranging symptoms. Radiological imaging assesses the pathological effects of abnormal thyroid function as well as important morphological features.

Nuclear scintigraphy provides functional information because of the ability of the radio-nuclides to be taken up by functioning thyroid tissue. Thin section CT and MRI can demonstrate the tissue nature and enhancement characteristics of a large neck mass, especially if it extends into the mediastinum. High resolution US demonstrates clearly the anatomy and morphology of the neck soft tissues and pathological processes involving the thyroid gland and cervical lymph nodes. Sonography can also be used to guide interventional procedures, including fine needle aspiration cytology and biopsy.

5.1. Anatomy & embryology

The thyroid gland develops from median and lateral anlagen. By the tenth week in utero, the right and left anlage fuse with the median anlage, resulting in the bilobed form of the gland. The thyroid gland descends from its place of origin, the foramen cecum at the base of the tongue, to its final destination in the anterior lower neck. The line of descent is represented by the remnant thyroglossal duct, along which residual thyroid tissue may be found. Cases of descent beyond the normal distance result to a mediastinal thyroid component.

The thyroid gland is normally located in the anterior lower neck. It consists of right and left lobes which are joined at the midline by a thin bridge of thyroid tissue called the isthmus. The isthmus drapes over the anterior trachea at the junction of middle and lower third of the gland. The thyroid is anterior to the longus colli and paraspinal musculature and deep to the strap muscles (Fig. 5.1). An accessory lobe, referred to as the pyramidal lobe, may be present in up to 50 per cent of people, which usually arises from the isthmus of the gland and extends superiorly.



FIG. 5.1. Plain radiograph of the soft tissues of neck showing tracheal compression due to thyroid enlargement due to cancer.

The thyroid gland has a rich vascular supply. There are paired superior and inferior thyroidal arteries which are branches of the external carotid arteries and thyrocervical trunks, respectively. The thyroidea ima is an inconstant vessel, arising directly from the aortic arch and helps to supply the inferior thyroid, when present. The thyroid is drained by superior and middle thyroidal veins that empty into the internal jugular vein, and by an inferior vein that drains into the inoiminate vein.

5.2. Imaging

5.2.1. Conventional radiology

The plain radiograph of the soft tissues of neck and thoracic inlet view is done to assess tracheal deviation/compression, and retrosternal extension of thyroid enlargement (Fig. 5.1). The presence of calcification (Fig. 5.2) bears no relationship to the presence of malignancy and is usually only related to the age of the nodule or to previous haemorrhage. The skeletal survey and chest X ray help to see metastases (Fig. 5.3). Barium swallow is done sometimes in cases of dysphasia (Fig. 5.4).



FIG. 5.2. Plain radiograph of the soft tissues of neck showing thyroid enlargement with multiple calcifications later developed cancer.

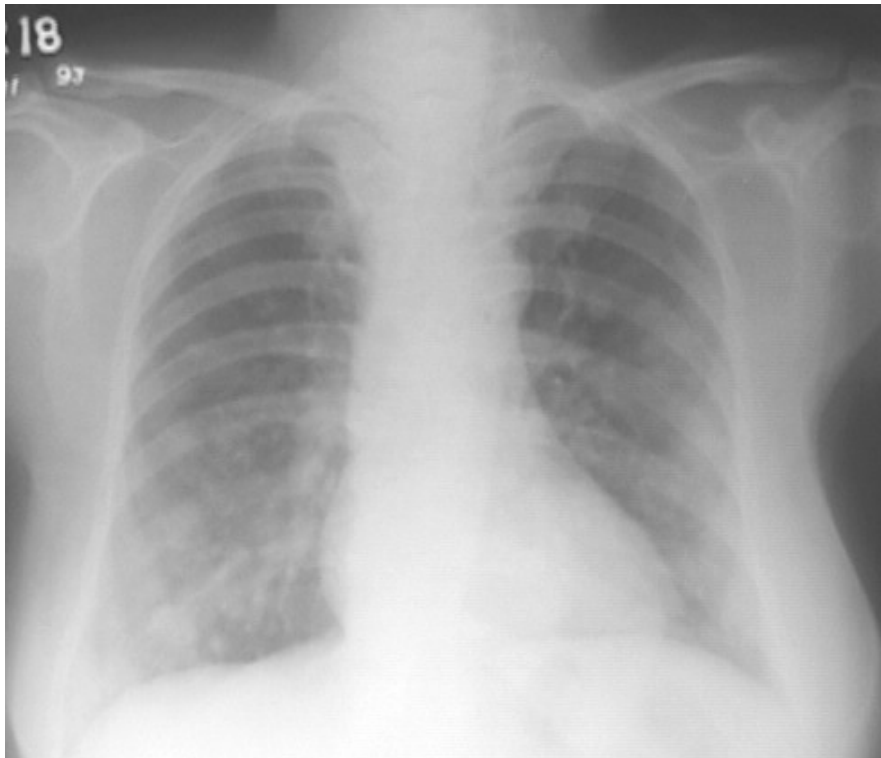


FIG. 5.3. Plain X ray chest showing multiple metastases due to follicular carcinoma thyroid.

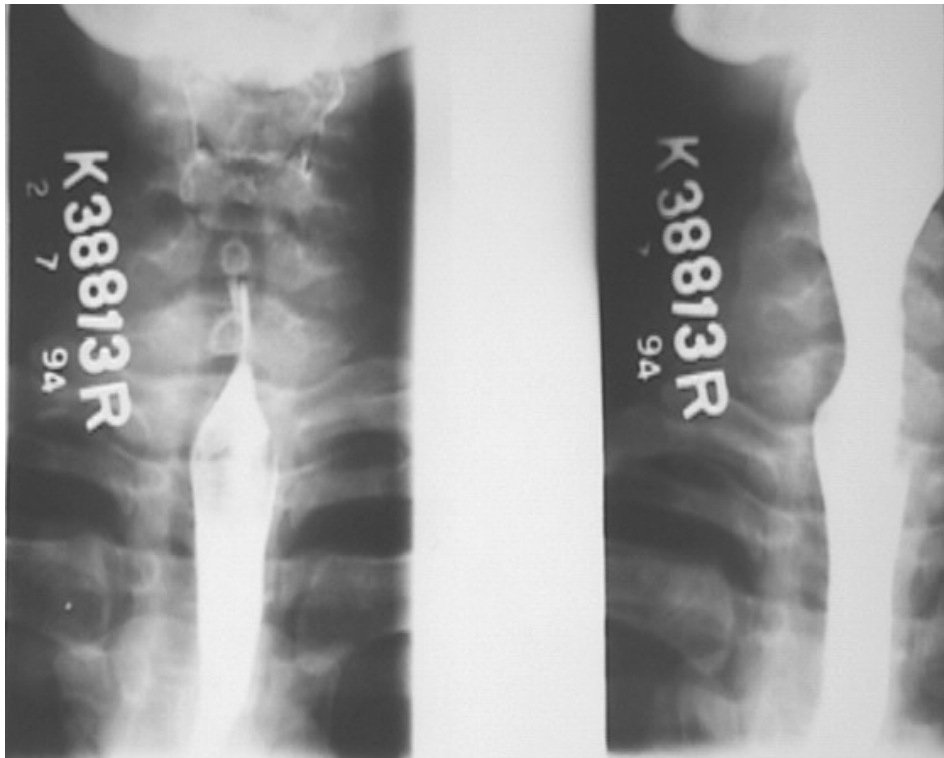


FIG. 5.4. Barium swallow in a patient of dysphagia showing extrinsic compression due to thyroid enlargement.

5.2.2. Ultrasonography

Being superficial in location, the thyroid gland is best seen by high-frequency sonography. Ultrasonography is generally the first choice for the evaluation of thyroid morphology because of its sensitivity for small nodule/mass detection. It is also used to assess the volume of thyroid tissue, to define the character and number of lesions, and to differentiate thyroidal masses from adjacent nonthyroidal masses like lymph nodes etc.

Real time ultrasound of the thyroid gland is usually performed with high-resolution linear array transducers ranging from 7 MHz or higher. With the patient in supine position, the neck is mildly hyperextended and the thyroid gland is scanned in its entirety in both transverse and longitudinal planes. The carotid arteries and jugular veins are posterior and lateral to the thyroid lobes, respectively, and provide excellent anatomic markers during the examination. Normal thyroid parenchyma has a characteristic sonographic appearance of homogeneous medium level echoes, with little identifiable internal architecture. The more hypoechoic a focal lesion is, relative to the normal thyroid gland, the higher is the likelihood of malignancy [5.2]. In selected patients, volume measurement may be helpful to confirm or quantify clinical suspected thyromegaly [5.3]. The use of colour Doppler imaging identifies multiple small vessels within and adjacent to the thyroid [5.1].

The major advantages of ultrasound are that it is accessible, inexpensive, and non-invasive. Because of the relatively short examination time required for ultrasound and the ability to image while the patient is taking thyroid hormonal supplementation, it is more convenient than scintigraphy for follow-up of patients with prior or increased risk of cancer. Improved grey scale and Doppler sonography have increased the accuracy and specificity of ultrasound

for thyroiditis and other diffuse glandular diseases [5.2]. Ultrasound-guided FNA can obviate the need for an expensive, long, and often non-diagnostic workup of a palpable nodule. In spite of these attributes, retrotracheal and mediastinal lesions remain difficult for ultrasound evaluation because of acoustic shadowing from overlying air or bone [5.1]. Another limitation of ultrasound is that it is inferior to cross-sectional imaging techniques in identifying lymphadenopathy or in evaluating for extension of thyroid disease into the soft tissues of the neck or chest [5.3].

5.2.3. Cross-sectional imaging

CT and MRI provide important adjunctive anatomic information. These modalities also play a critical role in the detection of lymph node metastases as well as in extension of thyroid disease to adjacent tissues in the neck like paraspinal muscles. Oesophageal, tracheal, and jugular vein invasion can also be assessed. CT and MRI are also useful for evaluation of mediastinal or retrotracheal extension of thyroid masses [5.1, 5.2].

For CT and MR examinations, patients are scanned in the supine position with the neck mildly hyper-extended. The patient is scanned with quiet breathing and suspended swallowing. Contiguous 5 mm-thick axial sections are obtained at the level of the cavernous sinus superiorly and extend inferiorly into the superior mediastinum to include the aortic arch. When small lesions are being evaluated, thin section may be obtained [5.2].

The normal thyroid gland has a density of approximately 80 to 100 Hounsfield units on CT. The injection of iodinated contrast material intravenously increases the density of the gland diffusely. Although iodinated contrast material may provide additional information about lesions in the thyroid, it alters radioactive iodine uptake measurements for 6 to 8 weeks because of the iodine content. Therefore, contrast should not be administered to patients who will also undergo scintigraphic evaluation. If both functional and enhanced cross-sectional anatomic studies are believed to be necessary, nuclear imaging can be performed before CT. Alternatively, MR with contrast (gadolinium) may be used because this contrast agent does not interfere with iodide uptake by the thyroid [5.2].

MRI is performed with a dedicated surface coil centred over the thyroid gland. This configuration provides high-quality images with a high signal-to-noise ratio and the best soft tissue resolution. Multiple pulse sequences are obtained including un-enhanced sagittal and axial T1-weighted images, as well as axial fast spin-echo T2-weighted imaged with the application of fat saturation. After the administration of intravenous gadolinium the gland enhances diffusely. On T1-weighted images, the normal thyroid gland shows homogeneous signal intensity slightly greater than that of the musculature in the neck. On T2-weighted images, the thyroid gland is hyperintense relative to the neck musculature [5.3].

5.2.4. Percutaneous aspiration and biopsy

Ultrasound guided fine-needle aspiration biopsy has been proposed as an alternative to conventional FNAB, particularly when FNAB is inconclusive. It offers the advantage of precisely targeting solid components within complex lesions [5.4].

5.3. Malignant neoplasms

Thyroid carcinoma arises from both follicular and parafollicular C cells. The potential of malignancy range from low grades (papillary/follicular carcinoma) to aggressive (anaplastic carcinoma). The major histological classification of thyroid carcinoma includes papillary,

follicular, medullary, and anaplastic. The majority of carcinomas (60 to 80%) are papillary, followed by 15-20% follicular, medullary and anaplastic types account from 5 to 10 per cent each of thyroid cancers [5.5, 5.6].

Most thyroid malignancy is hypoechoic (63%) or isoechoic (26%) on sonography; hyperechoic thyroid lesions tend to be benign [5.7]. Calcification causing bright hyperechoic foci, which if large enough cause acoustic shadowing, occurs in both benign and malignant disease [5.8]. Most commonly, thyroid cancer is a localized intrathyroidal hypoechoic or isoechoic discrete mass which is similar to more common benign lesions. The ipsilateral adenopathy in the neck raises suspicion of thyroid malignancy [5.9]. Large chunks of calcification in a thyroid mass suggest medullary thyroid cancer. Malignant invasion of the thyroid rarely may cause direct invasion of the carotid artery or local invasion of the adjacent muscles with loss of the normal tissue boundaries.

5.3.1. Papillary carcinoma

Papillary carcinoma is a low-grade malignancy occurring most commonly in adolescent girls and young adults. Frequently, papillary carcinoma is multi-focal in the thyroid gland and is thought to represent intraglandular spread rather than multiple synchronous tumours. It has the highest incidence among thyroid malignancies for cervical lymph node spread [5.10]. Metastatic lymph nodes may be normal in size and may be cystic, calcified or haemorrhagic, or they may contain colloid (Figs 5.5(a)-(c) and 5.6).

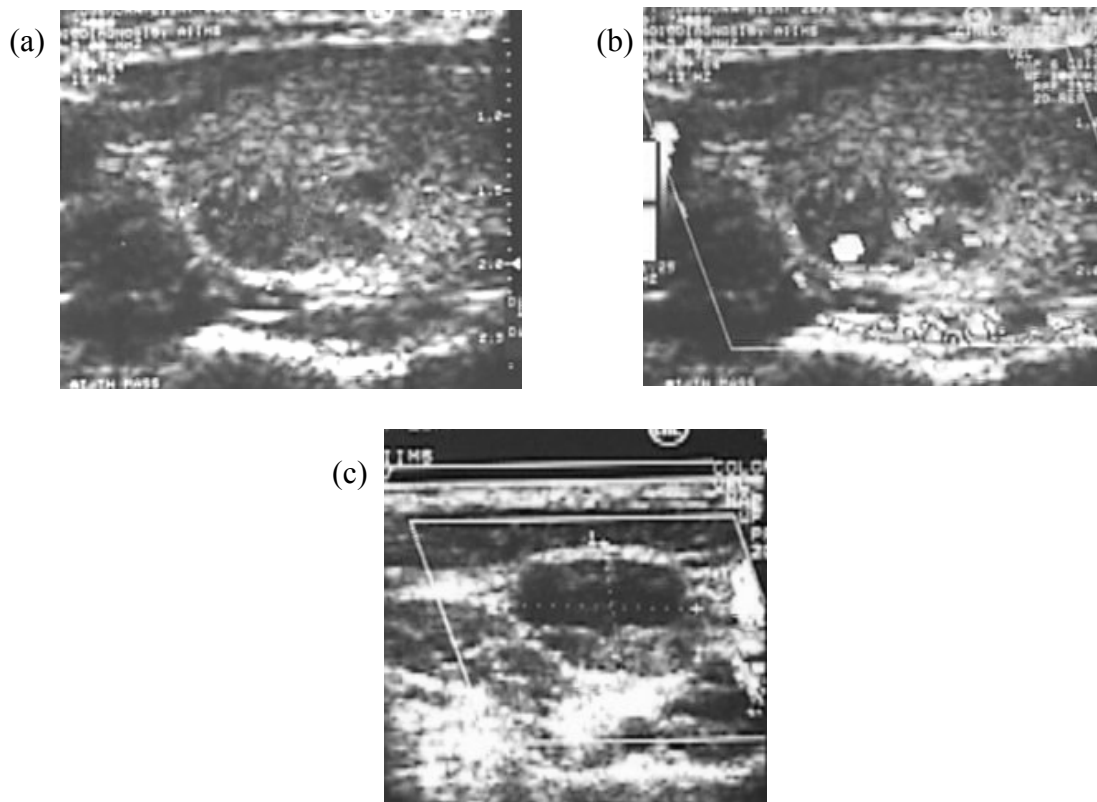


FIG. 5.5. (a) Hypoechoic mass in right lobe of thyroid, (b) showing vascularity on colour doppler, (c) with ipsilateral sonolucent lymph nodes, in a biopsy proven case of papillary carcinoma thyroid.

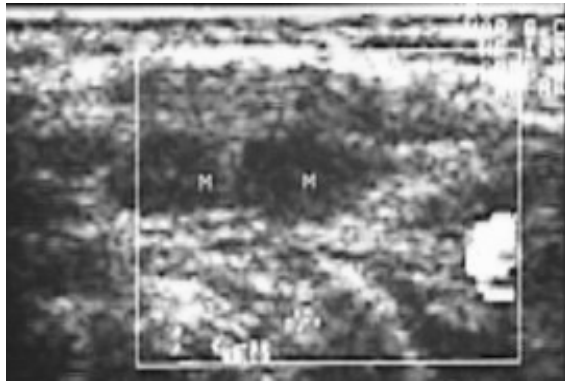


FIG. 5.6. Multiple hypoechoic masses in a case of papillary carcinoma thyroid.

5.3.2. Follicular carcinomas

Follicular carcinomas are well-differentiated, relatively low-grade malignancies. Pathologically, they are characterized by capsular and vascular invasion and are usually solitary lesions. Distant metastases to the lung and bone, related to haematogenous seeding, are more common than lymph node spread [5.10] (Fig. 5.7).



FIG. 5.7. Cystic thyroid mass with papillary projections. Biopsy — follicular carcinoma.

5.3.3. Medullary carcinoma

Medullary carcinoma arises from parafollicular C cells. It is relatively uncommon and has a higher mortality rate than well-differentiated papillary and follicular malignancies. Medullary carcinomas usually are solitary lesions; they may invade locally, spread to regional lymph nodes, and/or result in haematogenous seeding with distant metastases.

Medullary carcinoma occurs sporadically in 60-80% of cases, but it also may be inherited as an autosomal dominant trait, and it comprises a component of the multiple endocrine neoplasm syndromes [5.10], when the patient has known multiple endocrine neoplasms. Large chunks of calcification in a thyroid mass suggest medullary thyroid cancer and such calcification in cervical adenopathy suggest metastases from that source.

5.3.4. Anaplastic carcinoma

Anaplastic carcinoma usually presents in elderly women and is highly aggressive. It commonly occurs in patients with long-standing goitre (Fig. 5.8). These cancers grow rapidly and compress and invade the aerodigestive tract and vessels. Lymphatic metastases occur in the majority of patients and are often necrotic. On ultrasound they are often hypoechoic [5.3, 5.9]. The punctate calcifications and necrosis are present frequently on CT [5.3].



FIG. 5.8. Cystic thyroid mass with solid component. Biopsy-Anaplastic carcinoma developed in a long-standing nodule.

5.3.5. Primary lymphoma

Primary lymphoma of the thyroid gland is uncommon and usually presents in elderly women with a long history of goitre. Patients with Hashimoto's thyroiditis have an increased incidence of developing lymphoma of the thyroid, which usually is non-Hodgkin's in nature. Usually it presents as a solitary mass which is hypoechoic on ultrasound and hypodense on CT. Necrosis and calcification are uncommon [5.2].

5.3.6. Metastatic disease

Metastatic disease to the thyroid gland is uncommon [5.10]. Bilateral or unilateral enlargement of the thyroid, often with heterogeneity may be related to metastases to the thyroid from such sources as bronchogenic carcinoma, malignant melanoma, and renal cell carcinoma. Multiple thyroid masses are usually present in metastatic disease [5.3, 5.11].

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6. FUNCTIONAL EVALUATION OF THYROID

6.1. Introduction

A thyroid nodule is a very common condition (clinical and radiological prevalence of 7% and 40%, respectively) that may alarm the physician of the possibility of harbouring carcinoma of the thyroid. The latter, however, is a rare endocrine tumour with a yearly incidence of 0.004% that is significantly lower than the estimated incidence of a thyroid nodule of 0.1%. It is therefore essential to be able to separate benign from malignant nodules through clinical assessment and the combined use of non-invasive tests and simple needle aspiration.

6.2. Referral patterns

Patients are commonly referred for thyroid assessment for one or more of the following reasons:

- Presence of a palpable nodule
- Noticeable enlargement of the gland, either diffuse or nodular
- Signs and/or symptoms suspicious of malignancy that include stridor, hoarseness, lymphadenopathy, etc.
- Occasionally, a chest X ray or other imaging technique, performed for a different purpose, may show an abnormality of the thyroid size or shape or the presence of calcification that requires further clarification.

6.3. Clinical assessment

There is no substitute for good history taking and clinical examination. Certain features will give clinical clues to the possible nature of a nodule. Benign features include diffuse enlargement or a multinodular goitre in an adolescent or middle aged female, family history of benign goitre, constant size over time or decreasing size with thyroxine treatment. Malignancy should be suspected if the patient is aged <14 or >65 years of age, particularly in males presenting with a solitary nodule that is hard and fixed, specially in association with the suspicious features mentioned above or a history of radiotherapy to the neck.

6.4. Investigations

Once an initial diagnosis is established, further information can be obtained by the individual or combined use of scintigraphy with Technetium-99m- pertechnetate ($^{99m}\text{TcO}_4$), fine needle aspiration (FNA) and ultrasound scan (USS). The choice and sequence of these tests depend on availability, prevalence of specific thyroid disease, expertise and financial restraints. An initial approach with assessment of thyroid stimulating hormone (TSH) and scintigraphy is adopted in the presence of needle phobia, lack of expertise in FNA, bleeding tendencies or clinical signs of toxicity.

Alternatively, USS guided FNA is preferred when there are suspicious features such as lymphadenopathy or cord paralysis, in pregnant women and after recent use of contrast agents. USS provides excellent anatomical but non-functional details of a nodule. FNA have a variable sensitivity and specificity and is non-diagnostic in follicular tumours. Both are extremely operator-dependant and require high skills. In certain localities, and despite high sensitivity, use of FNA is non cost-effective due to high incidence of autonomous nodules [6.1].

Adding data obtained from these tests should establish a diagnosis in the majority of cases. A malignant hot nodule is extremely rare. A cold nodule that shows features of a small cyst on USS and benign features on FNA may be left alone, while a large and complex cyst or a MNG with a dominant nodule may raise suspicion of malignancy. In a minority of patients, further assessments with Thallium-201-chloride (^{201}Tl) or $^{99\text{m}}\text{Tc}$ - methoxyisobutylisonitrile ($^{99\text{m}}\text{Tc}$ -MIBI), or cross sectional imaging with CT or MRI may be necessary. When benign nature of a nodule cannot be established with certainty, tissue characterisation is mandatory requiring repeated FNA or surgical excision.

6.5. Radionuclide studies

The most common and practical method for thyroid scintigraphy is gamma camera planar imaging using $^{99\text{m}}\text{TcO}_4$. The mechanism of uptake is trapping of 3-4% of the administered activity, usually 75 MBq which produces good quality images. $^{99\text{m}}\text{TcO}_4$ undergoes no further metabolic degradation in the thyroid cells. A more physiological approach to thyroid imaging would involve a radioisotope of iodine that is both trapped and organified by follicular cells, commonly Iodine-123-iodide (^{123}I) and Iodine-131-iodide (^{131}I).

Unfortunately, ^{131}I both and ^{123}I have logistic and physical limitations that make their routine use in clinical thyroid scintigraphy somewhat unpractical. ^{123}I has pure gamma emission of 159 KeV and is ideal for in vivo gamma camera imaging with a reasonable half-life of 13 hours, but is a cyclotron product and therefore not universally available and relatively expensive. Radioiodine ^{131}I was the original radiopharmaceutical for thyroid imaging but has been superseded by $^{99\text{m}}\text{TcO}_4$ due to its higher gamma emission of 364 KeV and long half-life of 8 days leading to noisy images and un-necessary high radiation burden. It has retained its imaging function in post-surgical follow-up of differentiated thyroid carcinoma in addition to its therapeutic function that stems from its beta emissions. Table 6.1 shows the different characteristics of these radiopharmaceuticals.

TABLE 6.1. CHARACTERISTIC OF RADIOPHARMACEUTICALS USED FOR THYROID SCINTIGRAPHY

Radiopharmaceutical	T1/2	E (KeV)	Dose	Comments
$^{99\text{m}}\text{TcO}_4$	6 hours	140	74-185 MBq	Not physiological but cheap and available
^{123}I	13 hours	159	185 MBq	Ideal but not available universally & expensive, requires dietary restriction
^{131}I	8 days	364	37 MBq	Cheap but imaging is noisy with high radiation dose. Requires dietary restriction. Good for therapy and follow-up in differentiated thyroid carcinoma

Other radiopharmaceuticals, with different mechanism of uptake, include ^{201}Tl or $^{99\text{m}}\text{Tc}$ -MIBI which is used in the assessment of cold nodules and post-surgical follow-up especially in non-iodine avid thyroid carcinoma.

6.5.1. *Imaging*

Gamma camera imaging produces good quality 2-dimensional representation of the distribution of radiopharmaceutical that can be greatly improved with pin-hole collimation. Very little preparation is needed but drinking some water before imaging can clear the confusion created by pharyngeal activity consequent to salivary excretion. Certain medications that interfere with trapping mechanism such as thyroxine, tertroxine, amiodarone and potassium perchlorate need to be stopped for variable intervals. Iodinated contrast agents produce undesirable saturation of sodium-iodide symporter that may persist for weeks particularly lipid soluble agents.

Anterior views are obtained 20 minutes after intravenous injection of 75-185 MBq $^{99m}\text{TcO}_4$ supplemented by oblique and lateral views and occasionally single photon emission tomography (SPECT). Although rectilinear scanners are still in common use, they are time consuming and less reliable than gamma camera with overall accuracy of 77% compared to 94% for pin-hole imaging [6.2].

6.5.2. *Interpretation*

Both ^{123}I and $^{99m}\text{TcO}_4$ are trapped by follicular thyroid cells, salivary glands, choroid plexus, gastric parietal cells and lactating mammary glands. Recognition of these sites is important when ectopia is suspected.

The commonly depicted uniform 'butterfly' shaped thyroid (Fig. 6.1) is not always seen, as variations in size and shape of both lobes are not uncommon.

The various abnormalities noted on scintigraphy include:

- Diffuse enlargement or disparity in the size of the lobes
- Multinodularity with variable stages of hot and cold nodules (Fig. 6.2)
- Single nodule that may be cold (Fig. 6.3), warm or hot (autonomous) (Fig. 6.4)
- Non-visualisation of the thyroid or ectopia

In the context of thyroid carcinoma, the role of scintigraphy is mainly in the assessment of the functional status of a single thyroid nodule.

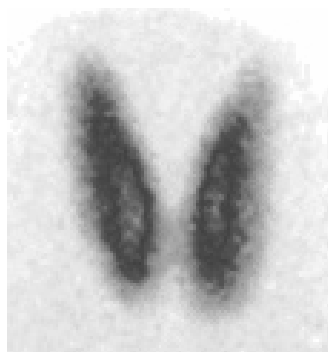


FIG. 6.1. $^{99m}\text{TcO}_4$ scintigram showing classic shape of the normal thyroid gland.

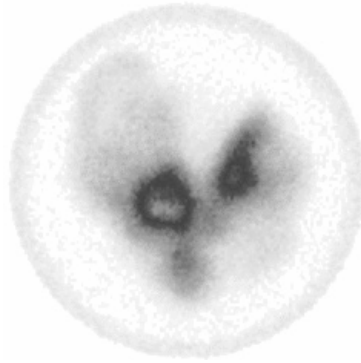


FIG. 6.2. $^{99m}\text{TcO}_4$ scintigram showing a multinodular goitre with variable nodule size and uptake.

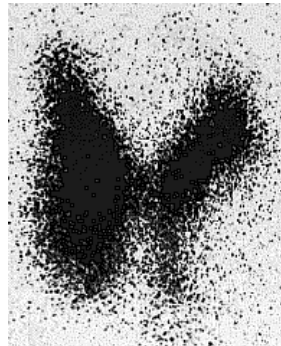


FIG. 6.3. $^{99m}\text{TcO}_4$ scintigram showing a cold nodule in the lower left lobe.

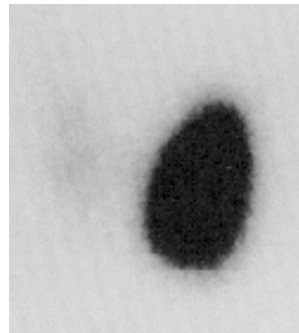


FIG. 6.4. $^{99m}\text{TcO}_4$ scintigram showing an autonomous nodule occupying most of the left lobe with suppression of the right lobe.

6.5.3. Scanning results of solitary nodules

Results of scintigraphy for solitary nodules reveal a cold nodule in the majority of cases (80-85%). However, only 5-10% of these are malignant. Other causes of cold nodules include thyroid cyst, localized subacute thyroiditis or Hashimoto's disease and benign adenomas. Warm nodules, with similar uptake to surrounding thyroid tissue, are seen in 10-15% of cases with a likelihood of malignancy of <10%. Hot Nodules constitute 5% of scanning results and were historically thought to have a likelihood of malignancy of <1%. There is, however, increasing evidence to suggest that this figure may be much higher. Smith, et al. [6.3] have shown an incidence of 6% in 30 patients over 25 years follow-up while others have shown an incidence of 44% of papillary carcinoma in a smaller group of 16 patients with shorter follow-up period of 5 years [6.4]. It is therefore prudent to carefully consider the malignant potential of hot nodules. There have been reports of nodules that are cold with ^{123}I but warm or even

hot on $^{99m}\text{TcO}_4$ [6.5]. This disparity is estimated to take place in 5% of cold nodules and some authors suggest repeating scans with ^{123}I in suspicious nodules that show normal uptake with $^{99m}\text{TcO}_4$.

6.5.4. *Imaging with ^{201}Tl and $^{99m}\text{Tc-MIBI}$*

Further assessment of cold nodules can be achieved by demonstrating uptake with some tumour detecting radiopharmaceuticals such as ^{201}Tl and $^{99m}\text{Tc-MIBI}$. Earlier reports demonstrated ^{201}Tl uptake in thyroid carcinoma but also in adenomas and thyroiditis [6.6, 6.7]. Tonami, et al. showed that if cold nodule was positive with ^{201}Tl , the statistical chance of the lesion being a cellular one was 100% with 55% risk of malignancy, while nodules with negative uptake had 14% chance of cellularity and a 7% risk of malignancy [6.6]. This approach was defined further by performing double-phased imaging showing washout of thallium from benign adenomas in delayed phase thus eliminating false positive results [6.8]. Some authors have disputed these results [6.9, 6.10] arguing that double-phased imaging will improve specificity at the cost of deterioration of sensitivity. Others suggested quantitation of lesion to non-lesion ratios as a better method [6.11]. Similar findings were reported using $^{99m}\text{Tc-MIBI}$ [6.12-6.14] and comparison of the two radiopharmaceuticals showed no significant difference in terms of sensitivity, specificity and accuracy in detecting malignant nodules when a retention index was calculated [6.15].

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7. FINE NEEDLE ASPIRATION BIOPSY OF THE THYROID

Fine needle aspiration biopsy (FNAB) is an effective, reliable and cost-effective technique for the diagnosis of thyroid cancer.

7.1. Indications

It's most prudent use is to investigate a suspicious thyroid mass that has been detected clinically or with the use of imaging techniques. In some countries with high incidence of thyroid cancer it has been used to investigate a prominent palpable mass before conventional thyroid scintigraphy or thyroid ultrasound [7.1-7.3]. The FNAB technique is relatively simple, quick and very cost-effective compared to more invasive tissue sampling techniques (Fig. 7.1). However, the FNAB test is most accurate when used as a complementary definitively diagnostic test following thyroid scintigraphy, and may be combined with thyroid ultrasound. An example of the cost-effectiveness of FNAB can be seen in hospitals where FNAB is widely accepted, as the number of thyroidectomy operations may drop by 20-50% [7.4, 7.5]. Furthermore, the proportion of cancers detected in nodules has been shown to increase from 8-20% to 40% since the advent of FNAB [7.5].

FNAB can also be utilized to distinguish between colloid goitre and autoimmune thyroiditis in diffuse non-toxic goitre. In addition, it can be used for confirmation of a clinically obvious malignancy, and to assess the nature of tissue and fluid cytology with the drainage of complex cystic lesions.

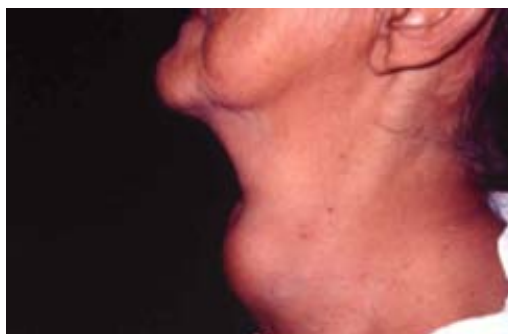


FIG .7.1. The solitary thyroid nodule is the most common indication for FNAB of the thyroid gland.

7.2. Contraindications

There are no contraindications to FNAB of the thyroid gland.

7.3. Complications

Bleeding is the most common complication and can be prevented by applying steady pressure over the FNAB site for at least 5 minutes. The trachea can also be punctured but this, at worst, will produce a coughing spasm that goes away within a few minutes. Although there were two reports of possible tumour seeding following FNAB of the thyroid [7.6, 7.7], this occurrence is exceedingly rare and does not seriously affect the patient [7.8].

7.4. Technique

7.4.1. Equipment

- Disposable plastic syringe, 10cc, with luer-lock tip, (Fig. 7.2)
- Disposable needles, 23-gauge, 1-inch long; Many operators prefer 25-gauge needles to lessen bleeding complications, but the use of a 23-gauge needle is often considered best to obtain optimal cellularity. A 22-gauge needle may be used to drain cystic lesions.
- Syringe holder — e.g. Cameco syringe pistol — This is not absolutely necessary but greatly facilitates the performance of the procedure. It enables the operator to use one hand for the syringe and needle, leaving the other hand free to fix the lesion (Fig. 7.3).
- Glass slides with frosted end
- Fixatives — 95% ethyl alcohol in Coplin jars, for wet fixation of smears; 10% buffered formalin for tissue fragments
- Cotton balls — dry and soaked in alcohol



FIG. 7.2. Shown are the aspiration gun, a 10cc syringe, and a choice of 22- or 23- gauge needles.

7.4.2. Patient preparation

- Put the patient at ease by explaining in simple terms the importance of the FNAB and how its result can influence his/her subsequent management.
- Give reassurance that the entire procedure takes only a few minutes, that the needle prick is less painful than a venipuncture and that no complications are expected.
- The procedure may be done either with the patient sitting down or in the supine position depending upon the size and depth of the lesion and the comfort of the patient.
- Caution the patient against moving, talking or swallowing once the needle is inserted.

7.4.3. The procedure

- Fix the thyroid mass between the second and third digits of the left hand (assuming the operator is right-handed).
- Introduce the needle through the skin into the nodule with the right hand, with the aid of a syringe holder.
- Once the needle is in place, apply suction gently.

- Move the needle back and forth; the angle of the needle may be slightly changed.
- When aspirated material or blood has filled needle hub, release suction. At this point, if the operator feels that he has gotten adequate material, he withdraws the needle. Otherwise, he may continue to move the needle back and forth even without negative pressure, a few more times before withdrawing the needle.

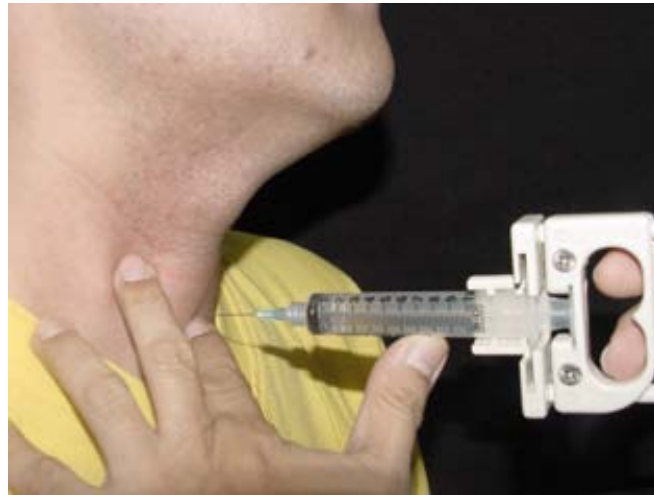


FIG. 7.3. The thyroid nodule is fixed by the second and third fingers of the left hand while the aspirator gun with the syringe is held with the right hand.

7.4.4. Making the smears

- Clean glass slides must have been laid out on the table even before the procedure is started. The fixative must also be at hand.
- Detach the needle from the syringe.
- Fill the syringe with air and re-attach the needle.
- With the bevel of the needle against the glass slide, squirt the contents on the glass slide.
- Put two glass slides together, press their contents in between them, and pull apart to make the smears.
- Drop smears promptly into the fixative (95% ethyl alcohol). Some smears may be air-dried for Diff-Quik stain.

7.5. Specimen adequacy

The definition of an adequate or satisfactory specimen from thyroid FNAB varies from institution to institution. According to Hamburger, et al. there should be at least six clusters of benign follicular epithelial cells in at least two slides from separate aspirates in order to diagnose a benign lesion [7.9]. Goellner, et al. are more explicit, requiring two to six groups of well-preserved, well-visualized follicular cells with each group containing ten or more cells [7.10]. However, the cellularity of a specimen depends on the intrinsic nature of the lesion from which it was taken. A benign colloid goitre often yields abundant colloid but few follicular cells. Cases such as this should not be considered unsatisfactory and may be diagnosed as 'consistent with colloid goitre' so long as it is qualified by the statement that the interpretation is 'limited by the paucity of the follicular cells'. This reporting approach is supported by the Papanicolaou Society of Cytopathology for the examination of fine needle aspiration specimen from thyroid nodules.

7.6. Reporting and clinical correlation

The cytological interpretation of a thyroid aspirate is categorized into:

- A. Benign lesions — colloid goitre, thyroiditis, cyst or cystic goitre
- B. Intermediate/Suspicious for malignancy — cellular follicular lesions, follicular neoplasms
- C. Malignant lesions — papillary carcinoma, anaplastic carcinoma, medullary carcinoma, malignant lymphoma
- D. Non-diagnostic/Unsatisfactory

Cellular follicular lesions include the hyperplastic nodule in an adenomatous goitre, the hyperplastic Hurthle cell nodule in Hashimoto's thyroiditis, the follicular adenoma, the well-differentiated follicular carcinoma and some cases of papillary carcinoma, follicular variant. It is not possible to differentiate between hyperplastic nodule in adenomatous goitre and a neoplasm in many cases because of their overlapping cytological features [7.11, 7.12]. It is possible, however, to give a diagnosis of 'cellular follicular lesion, favouring hyperplastic or adenomatous nodule'. In such a case, where the patient is considered to be low-risk, conservative medical management with close follow-up is advised. A hyperfunctioning nodule on radioisotope scan will also favour conservative management. A cell block preparation may help to distinguish follicular adenoma from colloid nodules [7.13]. Because the distinction between a follicular adenoma and a follicular carcinoma hinges on the histological assessment of capsular and/or vascular invasion, and because the cytological appearances of the two are similar, the FNAB cytological diagnosis is limited to 'consistent with a follicular neoplasm'. Some reports of large patient series have placed the proportion of follicular tumours detected by cytology at 70-90%, and of those, 14-40% have been ultimately diagnosed as carcinoma [7.14].

The difficulty in diagnosing the follicular variant of papillary carcinoma stems from the absence or rarity of papillary formations and the presence of follicular groupings (syncytial cell aggregates, microfollicles). However, a proportion of the cells exhibit the typical nuclear features (pale nuclei, powdery chromatin, nuclear inclusions, nuclear grooves) of papillary carcinoma.

In general, lesions in the category of indeterminate or suspicious require surgery for a definitive diagnosis. If the aspirate is less than optimal, a repeat FNAB may be indicated. A non-diagnostic or unsatisfactory aspirate is usually due to faulty technique of the operator or sampling error, i.e. the lesion is missed. A mastery of the skill in needle aspiration is as important as the proficiency in the interpretation of the smears. Other causes of unsatisfactory samples are inherent in the lesion and include sclerosis or fibrosis, a fibrous or calcified capsule, cystic degeneration and extensive necrosis. If a specimen is inadequate for interpretation, no diagnosis should be rendered on it by the cytopathologist and the information must be communicated to the clinician so that a repeat FNAB may be performed. For lesions that are less than one centimetre in size is difficult to palpate, FNAB may have to be done under ultrasound guidance [7.15].

7.7. Accuracy

A review of the literature shows that fine needle aspiration biopsy has an accuracy rate of 65-83%, sensitivity of 53-95% and specificity of 52-100% [7.16]. The most accurate results are obtained when an experienced cytopathologist performs the biopsy, primarily since sample

adequacy can be readily assessed [7.17]. The simplicity of the test, however, allows good results even when the procedure is done by clinicians, particularly when there is close coordination between the clinician and the cytopathologist.

It is common experience that optimal results and greater accuracy are achieved when the cytologic findings are correlated with clinical and radiological findings and when repeat FNAB's are done in the course of following-up patients with a benign diagnosis, or for cases that are indeterminate.

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8. PROGNOSTIC FACTORS AND RISK GROUP ANALYSES IN DIFFERENTIATED THYROID CARCINOMA

Primary thyroid tumours, although rare, are interesting to the clinicians and pathologists. From the clinical point of view, a majority of these tumours classified as differentiated follicular-derived thyroid carcinomas (DTC) are slow growing and show indolent biological behaviour, whereas, a small proportion of tumours classified as anaplastic carcinoma are highly aggressive tumours and can lead to death within few months after diagnosis [8.1, 8.2]. Papillary carcinoma, the most common of all thyroid tumours can exhibit different growth patterns and thus is classified into various subtypes, the majority behaves in an indolent fashion, and however, some have been shown to be aggressive in their clinical course [8.2, 8.3]. Several publications have specifically presented clinicopathological features [8.4-8.8] and molecular biological changes to identify the prognostic factors in thyroid tumours [8.9, 8.10]. A majority of these studies are based on prognostic factors in DTC with conflicting results, due to variations in criteria used for patient selection, pathologic classification and treatment modalities. However, despite conflicting results these studies have provided data so as to divide patients into sub-groups with similar prognosis and for selection of treatment modalities with lower morbidity.

8.1. Prognostic factors in DTC

The prognostic factors in DTC can be divided into clinico-pathologic factors and biological factors.

8.2. Clinico-pathological prognostic factors

Several authors have studied various clinical factors in large groups of patients and have devised treatment and prognostic schemes based on these factors. Most studies use cancer-related death as an end point. Because tumour recurrence rates reflect cancer related clinical problems, it is unfortunate that this parameter has not been well examined. Various clinical parameters used in these studies are:

8.2.1. Age

Age at tumour diagnosis has been found to be the most important prognostic factor in DTC [8.4, 8.11, 8.12]. It is shown that there is a linear increase in tumour recurrence and death with age, especially after age 40. Older patients often present with more aggressive tumours, more frequent distant metastases, and aggressive histological variants, thus leading to an unfavourable disease course [8.4, 8.5]. Children above the age of 10 and adolescents have an excellent prognosis even in the presence of extensive local disease and distant metastasis. However, children under 10 years of age with DTC usually exhibit more advanced disease and a high risk of disease-related mortality than children over 10 years of age [8.11, 8.13-8.15].

8.2.2. Gender

Tumours in men follow a more aggressive clinical course compared to women [8.7, 8.16]. A study of 1257 patients by Lin, et al. [8.16] showed that male patients with papillary carcinoma were more prone to distant metastasis. These results were also corroborated by a Canadian study of 1578 patients [8.17]. However, some large studies have failed to show any correlation between gender and prognosis of DTC [8.4, 8.5].

8.2.3. Size

The size of papillary carcinoma of thyroid can range from less than 1 cm to a tumour replacing the entire thyroid lobe [8.1, 8.2, 8.13]. Tumours measuring less than 1 cm or less are defined as microcarcinoma by the World Health Organization (WHO) [8.18]. It has been shown that tumour size is a dependable prognostic factor in DTC (19). Although papillary microcarcinoma rarely show nodal metastases [8.20] while large tumours (4 cm or more) are often associated with extrathyroidal extension [8.16]. However, it is unclear from published studies that tumour extension rather than size is an important factor affecting the prognosis.

8.2.4. Multifocality

In cases of papillary cancer, multiple foci of tumour may be present within one lobe or both lobes [8.2, 8.21]. This is a cited reason for total thyroidectomy in patients with papillary cancer [8.19, 8.22]. Some authors believe that these multiple foci represent intraglandular spread of tumour via lymphatics [8.1, 8.2] however, others have shown by *RET-PTC* analysis that these foci are separate tumours and not a progeny of one clone [8.23]. Multifocal tumours have an increased propensity to metastasise to lymph nodes, have persistent local disease, regional recurrences, distant metastases and mortality [8.2, 8.24].

8.2.5. Vascular invasion

Historically, this factor has not been analysed in detail as a prognostic factor in DTC especially in papillary cancers. Gardner, et al. [8.25] showed tumours associated with intrathyroidal and/or extrathyroidal vascular invasion are associated with an increased incidence of distant metastases and recurrence.

8.2.6. Extrathyroidal extension

Both papillary and follicular carcinoma can have extrathyroidal extension [8.1, 8.13]. It has been shown that tumours associated with gross extrathyroidal extension (noted by the surgeon or by preoperative evaluation) have a worse prognosis than those confined to the thyroid [8.5, 8.26]. A study from Memorial Sloan Kettering Cancer Centre of 931 patients found that on multivariate analysis, extrathyroidal extension is one of the adverse prognostic factors [8.27]. Similar findings have been reported from other large referral centres [8.28, 8.29].

8.2.7. Degree of tumour differentiation

Most DTC are low-grade tumours, thus, grading of these tumours has not been successful [8.6]. Some DTC can show focal areas of less differentiated tumour (solid growth, focal necrosis, mitoses), which have been denoted as foci of 'poorly differentiated' carcinoma. According to these reports the presence of significant amounts (>10% of tumour mass) of these foci may adversely affect patient prognosis [8.30].

8.2.8. Metastases

Lymph node metastases are more common in papillary carcinoma than in follicular carcinoma [8.1, 8.13]. The reported rates for lymph node involvement in papillary carcinoma can be as high as 80% [8.1, 8.13, 8.16]. Some studies have suggested that lymph node involvement in papillary carcinoma is an adverse prognostic factor, whereas, others have found no prognostic significance [8.4, 8.5, 8.7, 8.31]. Mazafferri, et al. [8.7] found lymph node involvement to be highly predictive of tumour recurrence and cancer-related death. Hughes, et al. [8.32] found

that nodal involvement was dependent on age at the time of tumour diagnosis and was not an independent prognostic factor. Miralle, et al. [8.33] suggested vascular invasion, male, absence of tumour capsule, and perithyroidal involvement as predictive of presence of nodal disease by univariate analysis. However, by multivariate analysis only absence of tumour capsule and perithyroidal tissue involvement was predictive of nodal disease. Distant metastases to lung and bones can also adversely affect prognosis in DTC. These are more common in follicular than papillary carcinoma [8.13, 8.24]. Ruegemer, et al. [8.34] showed that distal metastases had increased mortality rates (up to 75%) in cases of follicular and Hurthle cell carcinoma and 82% of these died of their disease within 5 years.

8.2.9. Treatment

Many thyroidologists and surgeons recommend that DTC should be treated by near-total thyroidectomy and ablation of the thyroid remnant by post-operative radioiodine (¹³¹I) treatment [8.7, 8.19, 8.35]. Near-total thyroidectomy is preferred by many clinicians over partial thyroidectomy because of the following: a) multicentricity in papillary cancer, b) frequent nodal disease, c) highly invasive nature of follicular carcinoma, and d) difficulty in ablation of large thyroid remnant by ¹³¹I. At present, there are several nonrandomized published reports which show that this treatment significantly reduces tumour recurrence, improves survival, and facilitates follow-up [8.7, 8.16, 8.19, 8.35, 8.36]. It has been shown that tumour recurrence can occur in thyroid remnant in 20% of patients and distant metastases are more common after subtotal than total thyroidectomy [8.35, 8.37, 8.38]. In light of these studies exploring the effects of mode of treatment on prognosis in DTC, many clinicians believe that an initial aggressive management may lead to disease free survival in more than 90% of patients [8.7, 8.39]. In young patients with small tumours (<1.5 cm), and no evidence of thyroid capsule invasion or metastases, a conservative approach has been recommended. Total thyroidectomy and radioiodine treatment have not been shown to improve prognosis in this low risk group of patients [8.28].

8.2.10. Tumour markers

Thyroglobulin (Tg) is expressed by all DTC therefore Tg measurement can be used as a postoperative tumour marker, especially when normal thyroid tissue has been eliminated by surgery or radioactive iodine ablation therapy. Postoperative Tg is usually measured during thyrotropin (TSH) stimulation (endogenous or recombinant TSH) and has been found to be more sensitive for detecting disease than basal Tg measurements. This method also indicates TSH sensitivity of the tumour. It has been shown that changes in serum Tg represent evolution of disease (change in tumour mass) after initial treatment [8.7, 8.40].

8.2.11. Tumour subtype

Papillary carcinoma is the most common form of DTC and patients with this tumour fare better than those with follicular thyroid carcinoma. The reported 10-year survival is 95% in papillary carcinoma and 80% in follicular carcinoma. However, this is dependent on histological subtypes of papillary carcinoma. In addition, survival figures in follicular carcinoma decline if Hurthle cell carcinomas are included. Despite these reported differences studies have shown that if the patients are stratified by their age and disease stage, survival curves for both papillary and follicular carcinoma are similar [8.2, 8.5, 8.7, 8.13, 8.41].

At present, numerous histological variants/subtypes of papillary carcinoma have been described but only few large series have an adequate follow-up to show an effect on

prognosis. A better prognosis is seen in encapsulated, cystic or microcarcinoma papillary cancer, whereas an aggressive clinical behaviour is seen in tall cell, columnar cell, and diffuse sclerosing variant [8.1, 8.2, 8.3, 8.13].

Tall cell variant of papillary carcinoma derives its name from the presence of elongated tumour cells (the height of individual cell being twice the width) with nuclear features of papillary carcinoma. Hawk and Hazard [8.42] initially reported this tumour in 1976. These tumours are usually of large size (>5 cm), present at older age and have a strong male predilection. These tumours exhibit a strong tendency toward extrathyroidal extension, vascular invasion, local recurrence, distant metastases and cause disease-associated death in about 25% of patients [8.1, 8.13, 8.43].

Columnar cell carcinoma is a unique variant of papillary carcinoma. It is characterized by papillary architecture and nuclear stratification with prominent subnuclear cytoplasmic vacuolation resembling early secretory endometrium [8.13]. These tumours usually are aggressive and exhibit extrathyroidal extension, regional and distant metastases and a fatal outcome [8.44]. Recently, an encapsulated variant of this tumour have been described. These tumours are confined to the thyroid and show better prognosis compared to the initially described cases [8.45, 8.46].

Papillary microcarcinoma is defined as tumour measuring 1 cm or less in size [8.18]. A majority of these tumours are incidental findings during autopsy examination of thyroid or histological examination of thyroid lobe(s) resected for benign thyroid disease or as a part of surgical dissection of tumours of neighbouring head and neck organs (i.e., larynx) [8.20, 8.47]. Papillary microcarcinoma can be seen as a unifocal or multi-focal disease [8.1, 8.47]. The latter have been shown to be commonly associated with lymph node metastases and local recurrences. Therefore, it is recommended that hemithyroidectomy is adequate for unifocal tumours, whereas, multifocal tumours should be treated by total thyroidectomy [8.13, 8.20, 8.48-8.50]. Lupoli, et al. [8.51] recently described a familial form of this tumour in seven patients of which five tumours were multifocal and three showed vascular invasion.

Diffuse sclerosing variant of papillary thyroid carcinoma is commonly encountered in children and adolescents. It involves the whole thyroid diffusely and also shows sclerosis, squamous metaplasia, tumour-associated lymphocytic infiltrate, abundant psammoma bodies, and marked lymphatic invasion. All patients affected by these tumour show nodal disease and up to 25% also have lung metastases. Because of its clinical presentation some authors classify this tumour as an aggressive form of papillary thyroid carcinoma, whereas, other believe that it behaves like the usual papillary thyroid carcinoma [8.52].

Hurthle cell carcinoma is a variant of follicular carcinoma, which is predominantly or solely composed of oncocytic cells (at least 75%). These, tumours are frequently associated with extrathyroidal extension and with both distant and nodal metastases. Several studies have shown that Hurthle cell carcinoma is a more aggressive tumour and follows a less favourable clinical course than follicular carcinoma [8.53-8.57].

In encapsulated carcinoma, up to 14% of papillary carcinoma can be encapsulated [8.1, 8.13]. These tumours consist of either pure papillary, follicular, or a mixture of both growth patterns. Usually the tumour capsule is thick, can show dystrophic calcifications and there is no evidence of capsular and/or vascular invasion [8.1, 8.13]. The nuclear features make the diagnosis of papillary carcinoma possible. It is generally believed that these tumours follow an indolent clinical course [8.1, 8.2, 8.3, 8.13, 8.8, 8.59]. These tumours can be associated

with lymph node metastases, however, local recurrence and metastatic spread is uncommon [8.3].

The diagnosis of follicular carcinoma is dependent on the presence of capsular and/or vascular invasion [8.1]. Some authors believe that the follicular carcinoma diagnosis should only be made in the presence of vascular invasion only [8.60]. Khan and Perzin [8.61], in their study of follicular tumours found that capsular invasion without vascular invasion was associated with metastatic disease. Evans [8.62] has reported similar findings. Therefore, follicular tumours showing only capsular invasion should be diagnosed as 'minimally invasive follicular carcinoma' and tumours with vascular invasion are termed as 'angio-invasive follicular carcinoma'. The angio-invasive tumours lead to haematogenous metastasis to bone and lungs, causing death in 50% of patients at 10-year follow-up. In contrast, minimally invasive tumours have a minimal chance of metastasising. In general, compared to widely invasive follicular carcinoma that diffusely infiltrates the affected lobe or entire thyroid, the 10-year survival rates for encapsulated tumours range from 70% to 100% and for widely invasive type are 25% to 45% [8.1, 8.13, 8.62].

8.2.12. Autoimmune thyroid disease

Approximately one-third of cases of papillary cancer can arise in the background of lymphocytic thyroiditis or show a tumour associated lymphocytic infiltrate. Some studies have suggested that these associations can lead to favourable outcome. In addition, positive antithyroid antibodies can also be detected in up to 50% of cases of papillary cancer associated with a lymphocytic infiltrate and in 23% of patients with DTC. After treatment disappearance of these antibodies suggests a successful initial treatment, whereas, their persistence is indicative of persistent or recurrent disease [8.63, 8.64]. Some studies have shown that tumours arising on a background of Graves' disease have an aggressive clinical course. These are often multifocal, show invasion and have nodal, and distant metastases [8.65].

8.2.13. DNA ploidy

DNA aneuploidy indicates an adverse prognosis in papillary thyroid carcinoma. However, multivariate analysis has failed to substantiate its role as an independent prognostic indicator [8.66-8.68]. Some studies have shown that death and tumour recurrences are more common in patients with aneuploid Hurthle cell carcinomas [8.53, 8.66].

8.3. Biological factors

8.3.1. Oncogenes and DTC

Among various oncogenes studied in thyroid tumours, RET/PTC oncogenes are uniquely restricted to papillary carcinoma. RET/PTC was first extracted from a metastatic papillary cancer as a mutated proto-oncogene, which could transform NIH 3t3 cells [8.69, 8.70]. Its prevalence ranges from 3-35% in spontaneous papillary thyroid carcinoma depending upon geographic location, however, it is expressed in up to 70% of radiation induced papillary cancers [8.71, 8.72].

The RET/PTC oncogenes are rearranged forms of the RET proto-oncogene (RET); to date, eight fusion proteins, RET/PTC 1-8, have been described, each of these functions by causing transposition of a cellular gene adjacent to tyrosine kinase domain of RET (RET TK). All of

these have been implicated in the early stages of PTC. Three different activating genes, H4 (D10S170 locus), R1 α , and ele1 have been shown to rearrange with RET to form RET/PTC1, RET/PTC2, and RET/PTC3 respectively [8.69, 8.73-8.79]. The sporadic papillary cancers most commonly express RET/PTC1 followed by RET/PTC2 and RET/PTC4 [8.9, 8.78, 8.79]. RET/PTC3 is more commonly expressed (up to 80%) in solid papillary tumours, especially the radiation-induced tumours seen in the Chernobyl reactor accident [8.71]. In addition, RET/PTC5 is also expressed in radiation-induced tumours [8.71]. Several investigators have suggested that RET/PTC leads to the development of papillary carcinoma. Cho, et al. [8.80] have shown that targeted expression of RET/PTC1 in the thyroid gland of transgenic mice causes thyroid carcinoma, which are morphologically similar to human papillary thyroid carcinoma. Tissue culture studies have shown that on induction of RET/PTC retroviral constructs into thyroid epithelial cells can lead to development of nuclear features of papillary thyroid carcinoma as compared to control cells or cells infected with H-ras gene [8.81]. In addition, thyroid glands from patients with Hashimoto's thyroiditis strongly express (up to 95%) RET/PTC1 and PTC3 without histopathological evidence of papillary thyroid carcinoma, indicating a possible risk of papillary cancer in these patients [8.82]. All these studies suggest that RET/PTC rearrangements represent an early event in the papillary cancer tumourigenesis but further studies are needed to define RET/PTC role in tumour progression and prognosis. There is a list of other genes, which have been studied in both follicular and papillary thyroid carcinoma, however, none of these have been found to be specific as RET/PTC. RAS-mutations have been noted in follicular adenoma and carcinoma [8.83, 8.84].

TABLE 8.1. STAGING OF THYROID CANCERS USING AMERICAN JOINT COMMISSION TNM CLASSIFICATION 2002 [8.87] (cont.)

Primary Tumour (T)

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- T1 Tumour 2 cm or less in greatest dimension, limited to the thyroid
- T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid
- T3 Tumour more than 4 cm in greatest dimension, limited to the thyroid or any tumour with minimal extrathyroidal extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)
- T4a Tumour of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve
- T4b Tumour invades prevertebral fascia or encases carotid artery or mediastinal vessels

All anaplastic carcinomas are considered T4 tumours

- T4a Intrathyroidal — surgically resectable
 - T4b Extrathyroidal extension — surgically unresectable
-

Regional Lymph Nodes (N)

Regional Lymph Nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

- N1a Metastasis to central compartment lymph node(s) or Level VI nodes
 N1b Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph node(s)
-

Distant Metastasis (M)

- MX Presence of distant metastasis cannot be assessed
 M0 No distant metastasis
 M1 Distant metastasis
-

Stage Grouping

Papillary or Follicular

	Under 45 Years	45 Years and Older
Stage I	Any T, Any N, M0	T1, N0, M0
Stage II	Any T, Any N, M1	T2, N0, M0
Stage III		T3, N0, M0
		T1-3, N1a, M0
Stage IVA		T4a, any N, M0
		T1-3, N1b, M0
Stage IVB		T4b, any N, M0
Stage IVC		Any T, any N, M1

Medullary

Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0
	T1-3, N1a, M0
Stage IVA	T4a, any N, M0
	T1-3, N1b, M0
Stage IVB	T4b, any N, M0
Stage IVC	Any T, any N, M1

All anaplastic carcinomas are considered as Stage IV

- Stage IVA — T4a, any N, M0
 Stage IVB — T4b, any N, M0
 Stage IVC — Any T, any N, M1
-

Activating mutations of thyrotropin receptor and a subunit of stimulatory G (Gs) protein gene has been found in some follicular adenomas and follicular carcinomas [8.85]. Inactivating

point mutations of the p53 gene are more commonly seen in poorly differentiated and anaplastic carcinomas [8.86].

8.4. Prognostic schemes

Several scoring systems have been devised on the basis of various prognostic factors. These systems present an algorithm to divide the patients into low- and high-risk groups for management purposes. None of the schemes is adequate in predicting outcome (and this may be the reason there are so many), but all stress the importance of age and extrathyroidal extension as prognostic factors including the latest TNM staging (see Table 8.1) system of AJCC 2002 [8.87]. Because the majority of thyroid cancers are indolent in clinical behaviour, these schemes are dissimilar from those predicting outcome in other human cancers. None of the current systems specifically includes histological tumour subtype, which may influence prognosis (i.e., tall cell variant papillary carcinoma).

First multivariate analysis in thyroid cancer was done by David P Byar, et al. (E.O.R.T.C Group) [8.88]. Factors studied in 500 patients were age at diagnosis, sex, histopathology, extent of primary tumour, lymph node status and systemic metastases. The contribution of the study was the development of a summary prognostic index, which could be used to predict survival of individual patients. The multivariate survival model (Weibull Model) showed that the important prognostic factors were: age at diagnosis, sex, principle cell type, T category (size of tumour) and systemic metastases. It had the disadvantages of a retrospective analysis and used complicated survival analyses methods. However, it was a good start in the right direction.

Cady, et al. [8.89] from Lahey clinic reviewed six hundred patients with primary differentiated thyroid carcinoma and follow-up of 15-45 years (from 1931-1960). They found that recurrence rate and death rate were significantly different in defined high-risk and low-risk groups of patients. These basic risk groups were defined by age and sex alone; low risk consisted of men 40 years of age and younger and women 50 years of age and younger whereas the high-risk group were older patients. Recurrence and death rates in patients at high risk were 33% and 27% while respective figures for patients at low risk were 11% and 4%. Basic risk group definition outweighed the effect of pathologic type, local disease extension, type of treatment, and site of recurrence or metastasis. For instance, radioactive iodine cured 70% of patients at low risk with metastatic disease but only 10% of patients at high risk. They further found that less aggressive biologic behaviour of thyroid cancer before the age of menopause implies that an oestrogen-rich milieu may alter the effects of initiating and promoting factors in carcinogenesis and therapeutic trials of oestrogen were suggested in progressive metastatic differentiated thyroid cancer.

Cady, et al. [8.28] offered another multifactorial system for the identification of low-risk patients who made up 89.4% of all patients seen between 1961 and 1980 and who had a death rate of only 1.8%. The resultant high-risk group constituted 11% of cases but carried a 46% mortality rate. The risk-group definition was completely clinical and was based on age, presence of distant metastases, and the size and extent of primary cancer. They defined Low Risk Group as a) all younger patients without distant metastases, b) all older patients with either intra thyroidal papillary cancer or minor tumour capsular involvement follicular carcinoma or primary cancers less than 5 cm in diameter and no distant metastases; and High Risk Group as a) all patients with distant metastases b) all older patients with extrathyroidal papillary cancer or major tumour capsular involvement follicular carcinoma, and c) primary cancers 5 cm in diameter or larger regardless of extent of disease. They concluded that it

could be used confidently at the operating table to select conservative surgical procedures in patients with negligible risk of death.

From a multivariate analysis of more than 14 200 patient-years experience with papillary thyroid carcinoma (PTC), Hay, et al. [8.90] from Mayo clinic devised a prognostic scoring system based on patient age, tumour grade, extent, and size (AGES). This scoring system could identify patients at increased risk of mortality and was employed as an adjustment variable for analyzing the role of different types of surgical treatment in 860 PTC patients. They divided the patients into four risk groups according to AGES score: The minimal risk group (1) had an AGES score of 3.99 or less. The high-risk groups (2, 3, & 4) had score of >4. Cancer mortality at 25 years in patients with an AGES score of 3.99 or less was 1% after ipsilateral lobectomy (n = 131) and 2% after bilateral resection (n = 603), whether subtotal or total (p = 0.15). Of patients with an AGES score of 4 or more, those who underwent lobectomy alone (n = 30) had a mortality rate from PTC at 25 years of 65%, while those undergoing bilateral resection (n = 86) had a lower rate of 35% (p = 0.06). For patients at minimal risk (score of 3.99 or less) of death, no improvement in survival was demonstrable when patients underwent more than ipsilateral lobectomy. However, in a subgroup (score of 4 or more) identified to be at significant risk of death, the survival after bilateral resection was much higher than after ipsilateral lobectomy alone. They found that in neither the "minimal" nor the "higher" risk subgroup was survival significantly improved by the performance of total thyroidectomy.

The same group [8.29] further reviewed 1779 patients with PTC (followed up for >26 000 patient-years), divided by treatment dates into 1940 to 1964 (n = 764) and 1965 to 1989 (n = 1015). The final model proposed by them included five variables, metastasis, age, completeness of resection, invasion, and size (MACIS). The final prognostic score was defined as $MACIS = 3.1$ (if aged ≤ 39 years) or $0.08 \times \text{age}$ (if aged ≥ 40 years), $+0.3 \times \text{tumour size}$ (in centimetres), $+1$ (if incompletely resected), $+1$ (if locally invasive), $+3$ (if distant metastases present). Twenty-year cause-specific survival rates for patients with MACIS less than 6, 6 to 6.99, 7 to 7.99, and 8+ were 99%, 89%, 56%, and 24%, respectively (p < 0.0001).

DeGroot and associates [8.91] from University of Chicago have described a staging system based on extent of disease and site of metastases evaluated by clinical findings with no consideration to age or tumour features (PTC and FTC). In this system the patients with only intrathyroidal disease were staged as class I, those with cervical lymph node metastases as class II, patients with invasive disease outside thyroid gland or presence of fixed structure in the neck which could not be easily resected as class III and those with distant metastases as class IV.

Mazzaferrri, et al. [8.92] from Ohio University have described a scoring system which is independent of age but dependent on the extent of disease, tumour size and presence of lymph node metastases, presence of multiple tumour and distant metastases (PTC and FTC). These authors have shown that age has a biphasic influence with higher recurrence rate at extreme ages, and therefore, excluded age from staging the disease. Stage I includes all patients with tumours <1.5 cm without local invasion and only intrathyroidal disease, while Stage II has patients with tumour size ranging from 1.5-4.4 cm, multiple tumours with no local invasion or metastases. Stage III constitutes patients with tumours greater than 4.5 cm, any nodal disease, any multiple tumours with invasive disease but no distant metastases, while patients with distant metastases with any other tumour features are included in Stage IV. In both De Groot

and Ohio classifications, Stages I and II are low risk while Stages III and IV are high risk groups.

A Canadian survey of thyroid cancer described 1074 patients with papillary thyroid cancer and 504 with follicular thyroid cancer followed for 4 to 24 years [8.17]. The study groups included more patients with 'advanced' disease and fewer with 'early' disease than in the general population. Although this report was subject to all the problems of retrospective studies, a careful assessment of the pre-treatment extent of disease combined with a long follow-up period had allowed an analysis of prognostic factors with considerable confidence. Univariate analysis of 12 possible prognostic factors (excluding treatment) demonstrated that 9 of them were of statistical significance: a) postoperative status, b) age at diagnosis, c) extrathyroidal invasion, d) distant metastases, e) nodal involvement, f) differentiation, g) sex, h) tumour size, and i) pathologic type (in descending order of importance). Multivariate analysis was carried out using cause-specific survival rates. Independently important prognostic factors at initial treatment were age at diagnosis, extrathyroidal invasion, and degree of differentiation histologically for papillary cancers, and extrathyroidal invasion, distant metastases, primary tumour size, nodal involvement, age at diagnosis, and postoperative status for follicular cancers. The prognostic factors for tumour recurrence were also quite different for the papillary and follicular cancers and ranked differently for the two groups.

A retrospective review of a consecutive series of 931 previously untreated patients with differentiated thyroid carcinoma treated over a 50-year period was undertaken by Shah, et al. from Memorial Sloan Kettering cancer centre to analyse prognostic factors [8.12]. Data pertaining to demographic status, clinical, operative, and pathologic findings, and survival were analysed. Univariate statistical analysis was performed based on the Kaplan-Meier method and the log-rank test. Multivariate analysis was performed to assess the independent effect of these variables using the Cox model. Favourable prognostic factors using univariate analysis included female gender, multifocal primary tumours, and regional lymph node metastases. Adverse prognostic factors included age over 45 years, follicular histology, extrathyroidal extension, tumour size exceeding 4 cm, and the presence of distant metastases. On multivariate analysis, the only factors that affected the prognosis were patient age, histology, tumour size, extrathyroidal extension, and distant metastases. Their observations supported findings of reports from the Mayo Clinic and Lahey Clinic regarding the significance of prognostic factors for differentiated carcinoma of the thyroid gland.

Shaha, et al. [8.27], also from the Memorial Sloan Kettering cancer centre, retrospectively reviewed 228 patients with follicular carcinoma of the thyroid. Various prognostic factors such as age, tumour stage, metastasis, histological type and grading and risk groups were analysed. Univariate and multivariate analyses were performed, and the survival curves were plotted by the Kaplan-Meier method. They divided patients into low, intermediate and high risk group. The 10-year survival for low, intermediate, and high risk groups was 98%, 88%, and 56%, respectively, and the 20-year survival for the same groups was 97%, 87%, and 49%, respectively. Adverse prognostic factors included age older than 45 years ($p < 0.001$), Hurthle cell variety ($p = 0.05$), extrathyroidal extension, tumour size exceeding 4 cm, and the presence or absence of distant metastasis ($p < 0.001$). Gender, focality, and presence of lymph node metastasis had no significant impact on prognosis.

Rao, et al. [8.93] undertook a retrospective study of follicular thyroid cancer operated at the Tata Memorial Hospital during the period 1970-1985, to define the prognostic factor. The variables age, sex, size, extrathyroidal spread, distant metastases, and lymph node metastases

were evaluated. They stratified the patients into low-risk and high-risk groups. The low-risk group included: age below 40 years, tumour size less than 5 cm. and no extrathyroidal extension or metastases. This low risk group had 100% survival at 15 years, compared with 40% survival for the high-risk group ($P < 0.001$).

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9. DIFFERENTIATED THYROID CANCER IN CHILDHOOD AND ADOLESCENCE

9.1. Introduction

Differentiated thyroid cancer (DTC) is a rare disease in the general population and very uncommon in children and adolescents [9.1]. Amongst all the malignancies in the paediatric age group the reported incidence of thyroid carcinoma is only 1-2% [9.2-9.6]. Thyroid cancer in the paediatric age group is reported to behave differently than in the adults. Age is an important prognostic factor in DTC with children carrying a better prognosis than the adults [9.7, 9.8]. Paradoxically thyroid cancer behaves more aggressively in the paediatric age group with higher incidence of cervical lymph node and distant metastasis at the time of diagnosis [9.6]. This paradox of being benign but with an aggressive natural history is unusual among childhood malignancies. In view of this strange combination of a benign outcome and aggressive course, there is no unanimity regarding the management of the disease. Some give credence to its benign nature and advocate a conservative approach to the type and extent of surgery without radioiodine (^{131}I) ablation for remnant thyroid tissue, while others believe that the tendency of the early spread of the disease necessitates a complete thyroidectomy followed by ^{131}I ablation [9.9]. Since there is difference in the presentation and outcome of DTC in children as compared to adults, there is a need for developing consensus in deciding the best management strategy in this subset of patients.

9.2. Incidence and epidemiology

The observed incidence of childhood DTC is from 1-10% as reported in published series (Table 9.1) [9.1, 9.4, 9.6, 9.10-9.29]. The incidence and mortality from DTC have markedly increased in children exposed to ionizing radiations either accidentally (after the Chernobyl accident or a nuclear fall out in the Marshall Islands) or by atomic bomb blasts (Hiroshima & Nagasaki) [9.33]. There is a definite increase in the overall incidence of thyroid cancer as reported by several investigators in these regions [9.34-9.36]. The study of thyroid cancer, particularly in children, gains special importance in view of this enhanced incidence after exposure to radiation. An overall ratio of females: males is 2-3:1.0. The female to male ratio is usually 0.5:1.0 for children younger than 11 years, 1.5:1 for 11-15 years and 2-3:1.0 for children above 15 years. This observed preponderance of females after the onset of puberty is more marked in papillary thyroid carcinoma (PTC) and less distinct in the follicular thyroid carcinoma (FTC). In girls, it is likely that the onset of puberty may activate and enhance thyroid carcinoma [9.10, 9.28, 9.37]. However, with increase in age, the gender difference is reduced.

9.3. Aetiology

Three causal factors have been reported to play a possible role in thyroid cancer. The first is exposure to radiation. Exposure of the neck to radiation in early childhood is the only known predisposing factor for thyroid neoplasia [9.38-9.40]. In some series, the history of radiation to the head & neck in childhood has been reported in 20-80% of the children with DTC [9.11, 9.20, 9.34, 9.44-9.42] in earlier studies when radiation was used to treat benign conditions. However, majority of cases are spontaneous and cannot be related to any specific cause [9.43].

The second is the high level of thyroid stimulating hormone (TSH). This finding was observed in animal models but is yet to be confirmed in humans; nevertheless, most thyroid

physicians prefer to maintain a low level of TSH in patients with thyroid cancer. No attempts have been made to differentiate between younger and older patients in this respect. Several studies have also reported an association between Hashimoto's thyroiditis and papillary carcinoma of thyroid. Although the numbers are far from convincing in the adult age group, the association is much stronger in children [9.44].

The third aetiological factor suggested, is a long period of iodine deficiency. However, in view of the observation that more than 25 years of iodine deficiency are required to affect this association, this factor does not appear to be relevant for the paediatric age group. However, the incidence of thyroid cancer in children and adolescents in this patients series from sub-Himalayan iodine deficient endemicia was 7%. It is on the higher side in comparison to reported incidence for non-radiation exposed children (from 2.96%, 3.05%, 7.5%, 9% and 10.1%) [9.12, 9.45-9.46].

9.4. Pathophysiology

The PTC is predominant in the younger age group. Although there is an apparent preponderance of females having PTC (F: M; 2.8: 1) as compared to FTC (F: M; 1.3:1), Buckwalter and his colleagues [9.12] have reported a higher incidence of PTC in younger males. The reported frequency varies between 35-95% for PTC and 5-54% for FTC (Table 9.1). The variable incidence of reported PTC/FTC tumours could be due to differences in classification where mixed variety is generally considered as PTC. It is believed that mixed group of tumours behave histologically as PTC. However, iodine deficiency might be associated with a higher number of follicular carcinoma [9.28].

Multicentric tumours are present in about 20% of paediatric cases indicating that the incidence of multicentric tumours in the younger age group is lower than that reported in adults. Multicentricity of the carcinoma involving at times both the lobes could vary from 20-81% (Table 9.1), especially when there is an evidence of extra-thyroidal or extra-nodal invasion [9.11, 9.22]. Invasive disease includes evidence of extra-thyroidal spread of the primary tumour as reported on histological findings, surgical evidence or during clinical examination. The invasiveness of the disease is significantly more in children and in elderly as compared to in adults. Amongst the children the invasiveness of primary tumour is lowest with intra-thyroidal disease, highest with lung involvement and in between with nodal disease [9.1, 9.4, 9.16, 9.19, 9.20, 9.22]. The reported incidence of positive family history for DTC is 3-4% [9.1, 9.19, 9.20, 9.27], which indicates that TC in children is seldom familial in nature.

9.5. Modes of presentation

9.5.1. Primary thyroid abnormality

Thyroid cancer in children and adolescents often presents as an advanced disease [9.4, 9.14, 9.19, 9.47, 9.48]. The predominant mode of presentation is a solitary thyroid nodule (STN). Nodules occur with equal frequency in both sexes across age groups and there is no predominance of either, papillary, follicular or mixed histological differentiation. The second most common presentation of primary thyroid disease is a MNG and uncommonly as a diffuse goitre, an ectopic thyroid or a normal thyroid.

9.5.2. Intra-thyroidal disease

The intra-thyroidal disease (absence of metastases) is usually significantly lower in children as compared to the middle age group (19-45 years) patients, but comparable to that seen in

elderly age above 45 years. This suggests that at extreme ages metastatic disease is more common.

9.5.3. Regional cervical (nodal) disease

The incidence of nodal metastases is highest in children as compared to that in middle age group and in the elderly group. The nodal metastases are present in 4-90% of the children [9.1, 9.4, 9.6, 9.17, 9.18-9.20, 9.46]. Of the total nodal metastases, around 30% have concomitant pulmonary metastases. The incidence of nodal metastatic disease is not age or sex dependent [9.1] but some have reported otherwise [9.6]. However, the tendency to metastasize appears to be higher amongst the younger male patients. The overall incidence of metastases in the pre-pubertal (less than 12 years) children is more than in the post-pubertal. Nodal metastasis is more frequent in MNG as well as isthmic nodules.

9.6. Distant metastasis

9.6.1. Pulmonary metastases

The incidence of lung metastases is significantly higher in children as compared to adults indicating an aggressive nature of the disease in the former group. In fact, younger the patient, more are the chances of pulmonary metastasis. The reported incidence of lung metastases in children varies from 5-42% [9.4, 9.6, 9.11, 9.15, 9.17, 9.49]. While such a high incidence of metastatic disease in lungs is associated with a high mortality in other oncological diseases of childhood, it does not hold true for thyroid carcinoma. The presences of bilateral cervical nodal metastases, especially with the involvement of lower cervical and supraclavicular nodes, should give rise to a high degree of suspicion for a possible lung involvement. PTC tends to metastasize more frequently to the lung than FTC.

9.6.2. Other systemic metastases

Distant metastasis in DTC is a rare event amongst the younger age group [9.10]. Thus, predilection of DTC to metastasize only in the lungs and not in any other body organs is at variance from other oncological diseases of childhood and from its behaviour in adults. In the latter, especially after the 4th decade the incidence of skeletal metastases is as high as 30-40%. Probably growing bone does not provide a suitable milieu for deposition of thyroid cancer cells. Another likely explanation could be that in contrast to adults in whom the metastatic spread is *via* the haematogenous route the children might have lymphatic spread. However, skeletal and brain metastasis have been reported in children, especially in very young children [9.28].

9.7. Diagnosis

In childhood the traditional diagnostic approach to thyroid nodules consists of clinical, laboratory, and imaging evaluations. A safe and accurate procedure is needed to promptly identify patients who require surgery. For a patient presenting with thyroid swelling, FNAB is considered the investigation of choice to detect thyroid malignancy. Corrias, et al. [9.50] found a positive correlation ($r= 0.90$; $P <0.0001$) between fine needle aspiration biopsy cytological findings and histological diagnoses. The sensitivity, specificity, and accuracy of fine needle aspiration biopsy, according to them, were 95%, 86.3%, and 90.4%, respectively. They concluded that fine needle aspiration biopsy is a safe technique even in childhood and

adolescence, offering the best sensitivity, specificity, and accuracy in detecting malignancy compared with conventional approaches.

9.7.1. *Detection of nodal metastases*

Nodal metastases from primary thyroid carcinoma can be detected in one of the several ways: (a) At the time of the initial presentation of the primary disease, a careful clinical examination is sufficient to detect almost 80% of patients with a confirmatory FNAB. If FNAB is inconclusive, a lymph node biopsy is indicated; (b) in a few cases it is detected at the time of surgery and confirmed by frozen section; (c) in a very small number of children with small lesions not detected clinically or surgically it is often diagnosed on whole body scintigram (WBS) either at the time of the first post-surgical investigation or later when the residual thyroid is ablated with ^{131}I therapy.

9.7.2. *Detection of pulmonary metastatic disease*

The reported incidents of pulmonary metastasis vary widely from 5-42%. This wide variation is due to the methods of investigation used and the rigour of post-surgical evaluation with ^{131}I in some or in all patients. If the chest X ray is the only modality to detect pulmonary metastases, it should yield a very low positivity rate, as very few children have macronodular metastases. If all children, after surgery, are evaluated with ^{131}I WBS, the rate of pulmonary metastases shall be very high, as occult ones will be picked up by this modality. Unlike adults where only 50-70% of lung metastases take up ^{131}I , in children almost all lesions pick up ^{131}I . This ability to take up ^{131}I is beneficial for subsequent therapy and monitoring.

9.8. Treatment strategies

9.8.1. *Surgical procedures in management of childhood disease*

Surgery still remains the intervention of choice (like with adults) however, the next few subsections provide more insight into areas of agreement and some of the controversies specific to childhood disease.

9.8.2. *Surgery for primary thyroid carcinoma*

Performance of total thyroidectomy or aggressive surgery for primary disease as well as local metastases varies widely from as low as 36-100% (Table 9.1), which reflects the prevailing uncertainty about the optimal approach to treatment of childhood disease. While there is a general agreement for total thyroidectomy for FTC [9.51-9.53], there is a great deal of controversy about the surgical management of PTC [9.54]. Some recommend total thyroidectomy because of the high incidence of multifocal disease leading to recurrences later in the residual gland after partial thyroidectomy. Others have observed no difference in the survival and recurrence rates among patients treated with either conservative or extensive surgery, even when there was a multifocal or an invasive tumour [9.3, 9.13, 9.16, 9.18, 9.22, 9.55]. Total thyroidectomy is further believed (a) to prevent the transformation to anaplastic type of residual thyroid tissue at a later stage [9.56] and (b) increase the detection of metastatic disease because of the absence of competing thyroid tissue and thereby early treatment with ^{131}I [9.1, 9.4, 9.17, 9.19, 9.48, 9.56-9.60]. Proponents of less aggressive surgery believe that PTC at an early stage has a low risk of relapse and claim that a lobectomy or a partial thyroidectomy is adequate. Nonetheless, as an initial primary treatment we recommend that total/near total thyroidectomy should be done.

TABLE 9.1. THYROID CANCER IN CHILDREN: DEMOGRAPHY, TREATMENT, FOLLOW-UP AND OUTCOME

Author (published series)	Total no.	Inci- dence (%)	Age years	FU years		TT ^c (%)	Compli- cation (%)	Sur- vival (%)	Rec (%)	% Incidence					Site of Disease No of pts given			% Ablation						
				M ^a	A ^b					Pap ^d	Foll ^e	Mix ^f	LI	Tumours (cm)	MF	R/R ^h	N ⁱ	PM ^j	R/R	N	PM			
Excelby and Frazell [9.13]	62	5.1	<16	-	-	3.2	32	92	-	35	25	40	-	-	-	-	-	8	-	-	50			
Liechty, et al. [9.14]	30	-	<17	-	-	93	50	93	-	53	17	27	37	-	-	30	-	6	-	-	100	93		
Buckwalter, et al. [9.15]	58	10.1	<21	10	11	50	50	98	7.4	35	54	11	-	33(<2.5)	67(>2.5)	-	-	-	-	-	-	-		
Withers, et al. [9.16]	20	-	-	8	-	55	15	90	25	-	-	-	-	-	-	-	-	0	100	0	0	0		
Zohar, et al. [9.17]	8	7.7	<20	-	-	75	-	100	0	75	-	25	38	-	-	50	-	0	3/3	0	0	100	0	
Goepfert, et al. [9.18]	74	-	<20	7.3	15	95	17	100	-	9.5	2.7	77	-	-	-	-	-	3	31	8	100	100	100	
Tallroth, et al. [9.19]	40	-	<21	-	22	30	48	95	13	85	7	-	50	-	-	-	-	20	NK ^k	NK	NK	NK	NK	
Schlumberger, et al. [9.20]	72	-	<17	13	-	40	29	90	34	70	5	25	67	40	60	81	-	25	9 ^l	-	26 ^m	NK	NK	
Zimmerman, et al. [9.9]	58	5.6	<17	28	-	36	41	93	12	-	-	-	24	9(<1)	81(>1)	-	-	85	-	-	-	-	-	
La Quaglia, et al. [9.21]	100	-	<18	20	-	46	46	100	35	36	7	54	-	-	-	22	-	22	22	-	-	NK	-	
Ceccarelli, et al. [9.22]	49	6.3	<19	-	7.7	100	51	98	28	90	8.2	-	36	-	-	-	-	100	25	14	9	100	66	33
Merrick and Hansen [9.7]	20	-	<20	-	9.1	76	23	100	25	55	-	30	53	18(<1)	85(>1)	-	-	21	-	3	2	-	100	100
Frankenthaler, et al. [9.23]	117	-	<20	-	15	-	1	100	29	12	9	79	33	-	-	-	-	46	-	54	-	-	NK	-
Mazzaferrri and Jhiang [24]	106	7.8	<20	-	16	-	-	98	40	-	-	-	-	-	-	-	-	25	-	-	-	-	-	-

Author	Total no.	Incidence (%)	Age years	FU years		TT ^e (%)	Complication (%)	Survival (%)	Rec (%)	% Incidence					% T/T ^g	Site of Disease No of pts given			% Ablation				
				M ^a	A ^b					Pap ^d	Foll ^e	Mix ^f	LI	Tumours (cm)		MF	R/R ^h	N ⁱ	PM ^j	R/R	N	PM	
Fassina, et al. [9.4]	56	4.0	<20	9.3	-	96	11	100	3.5	77	16	-	-	-	-	85	8	27	9	100	89	89	
Massimino, et al. [9.25]	20	-	<15	11	-	70	36	100	35	95	5	5	-	-	40	0	-	-	-	-	-	-	
Balazs, et al. [9.26]	36	6.0	<20	-	-	50	-	100	28	83	11	-	-	-	-	2.7	-	-	1	-	-	-	100
Dinauer, et al. [9.27, 9.115]	137 33	- ≤21	-	6.6 5	-	61 52	-	99 100	20 15	100 100	-	39	2.2	31	12	58 54	-	-	-	-	-	-	-
Segal, et al. [9.28]	58	6.8	<20	-	-	8.2	5	97	19	20	20	60	33	55	-	-	-	-	-	-	-	-	
Dense, et al. [9.29]	48	13	<20	5	7.7	0	40	100	0.5	85	13	19	1-4	-	67	13	16	2	100	100	100	100	
Samuel, et al. [9.30]	84	4.4	<19	-	6	77	12	96	5	46	23	11	22	32(<1.5)	20	69	20	35	15	95	94	43	
Bal, et al. [9.31]	80	7	<20	5	5	0	10	96	11	85	15	-	-	-	100	26	21	20	96	90	55	55	
Jarzab, et al. [9.32]	109	-	<17	5	5	74	17	100	-	71	29	-	-	-	69	60	-	10	97	97	97	97	

M= Median

A= Average

TT= Total Thyroidectomy

Pap= Papillary Carcinoma

Foll= Follicular Carcinoma

Mix= Papillo-follicular carcinoma, Invasion

T/T= treatment

R/R= Recurrent disease/Residual disease

N= nodal

PM= pulmonary

NK= Not Known

Includes Res+Nodal.

Includes recurrent metastatic disease.

9.8.3. Surgery for nodal metastases

As to the management of cervical nodal metastases, surgical removal of these nodes is generally advocated. However, the extent of the neck dissection for nodal clearance appears controversial. Restricted surgery for removal of the neck nodes has been suggested by some as the residual nodal disease left after conservative surgery can be effectively treated by ^{131}I , primarily because nodal disease in children concentrates ^{131}I avidly [9.15, 9.19]. Moreover, conservative procedures avoid surgical complications. However, Schlumberger, et al. [9.17] in a study in 72 children observed a high relapse rate in those in who limited surgery was performed. They advise that the surgery in children and adolescents should be similar to that in adults. In the absence of clinically palpable disease (about 33% of the patients have occult microscopic nodal involvement) a prophylactic neck nodal dissection had been recommended in the past. However, prophylactic neck nodal dissection has failed to prevent relapse in 22% of the cases [9.22]. If these nodes become palpable later, removal of nodal metastases at relapse has been considered as adequate salvage treatment. The current preference is not to perform prophylactic neck dissection.

9.8.4. Surgical morbidity

Radical neck dissection and total thyroidectomy are bound to lead to several complications. The major complications are permanent hypocalcemia due to hypoparathyroidism which occurs in 7-46% of children (Table 9.1). This variable incidence is due to improved surgical techniques and experiences gained by surgeons in procedures of total thyroidectomy [9.61]. Another major complication is permanent recurrent laryngeal nerve paralysis which is reported to be as high as 14% by La Quagila and associates [9.18]. These authors further report an 11% incidence of temporary tracheostomy. Some of the other major complications, which occur infrequently, are Horner's syndrome, facial nerve paralysis, tracheal stenosis and major bleeding. Some less important complications include minor bleeding, facial oedema, transient hypocalcemia, hypertrophied scar and transient recurrent laryngeal nerve paralysis. None of these is a contraindication to radical surgery.

9.9. Radioiodine treatment

Differentiated thyroid carcinoma in childhood has been considered to have a favourable prognosis. Radioiodine treatment has been therefore considered unnecessary by many investigators. As is evident from Table 9.1, most studies have used ^{131}I in selected cases, primarily for management of the metastatic disease or occasionally when the primary tumour is not completely resected. Radioiodine is therefore being advocated in cases where the tumour is invasive and unresectable and/or there are distant metastases. Moreover, ^{131}I therapy for ablating residual thyroid tissue is a subject of considerable controversy. Almost all children receive thyroxine suppression therapy after surgery.

9.9.1. Residual thyroid tissue

Low incidence of recurrences in children who have undergone total/near total thyroidectomy followed by ^{131}I therapy has been observed. The ablation of the residual thyroid tissue with ^{131}I is justified. In children, 50-80% of lung metastases are occult, in the sense that the chest X ray is normal, the patient is asymptomatic, and the disease is discovered either by pre-ablation ^{131}I WBS (or ^{123}I WBS) or, less frequently, on post-ablation WBS. In order to facilitate the ^{131}I concentration by pulmonary metastases it is mandatory to ablate the competing residual thyroid tissue left behind after surgery. As the primary tumour is invasive and the incidence of

metastases to nodes and lungs is high, the recurrence at a later stage could be avoided if the remnant tissue is ablated. In most of the cases ^{131}I treatment for residual thyroid tissue is effective with only a single therapy [9.28] and is totally safe.

9.9.2. Nodal metastases

The non-palpable cervical nodal metastases, if present after surgery, are responsive to ^{131}I and a complete response is seen in almost 66-100% of the cases [9.1, 9.4, 9.11, 9.15, 9.19]. Nodal disease can be cleared with 2-3 therapies with ^{131}I doses ranging from 3700-5500MBq (100-150 mCi) at a single setting. Incidence of nodal recurrence in ^{131}I treated patients is lower than the reported range of 24-34% in patients not given ^{131}I [9.6, 9.18, 9.20] In a series of 117 patients with nodal metastasis, Frankenthaler, et al. [9.20] have shown a higher rate of nodal recurrence in patients who are not treated with ^{131}I (35%) as compared to those who were treated with ^{131}I (14%).



FIG. 9.1 (a). Chest X ray of a post-surgical low dose WBS revealing pulmonary metastasis.

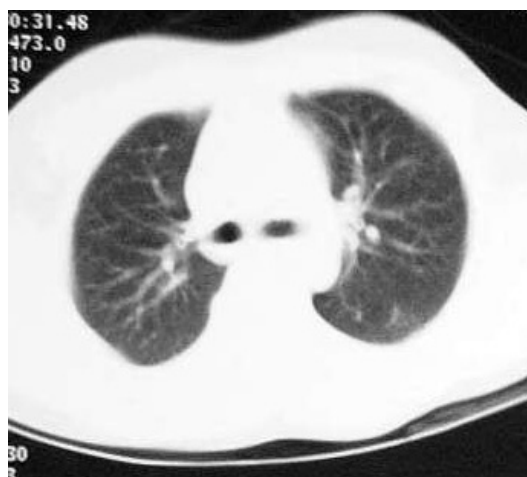


FIG. 9.1 (b). High resolution CT scan.

9.9.3. Pulmonary metastases

There is a greater consensus regarding the need to give ^{131}I for lung metastases in comparison with that of treating remnant thyroid tissue. Pulmonary metastatic disease can be cleared with 2-5 therapies with ^{131}I doses ranging from 3700-5500MBq (100-150 mCi) at a single setting. The response to ablation of lung metastases varies from 33-89%. It is known that ^{131}I concentration in clinically stable lung metastases may persist for many years [9.62, 9.63]. Although ^{131}I treatment for ablating residual tissue as well as pulmonary metastases has been found to be safe, several treatments over a number of years can rarely result in radiation-induced fibrosis leading to pulmonary insufficiency. The identification of end points for the administration of ^{131}I treatment with respect to the number of therapies is unclear and varies from one centre to another. Retrospectively, it appears that patients who have radiographically stable pulmonary metastases or minimal ^{131}I concentration may be monitored conservatively with thyroglobulin (Tg) measurement, chest X ray and pulmonary function tests without further ^{131}I therapy, albeit in children X ray is not a good modality to detect early disease in lungs.

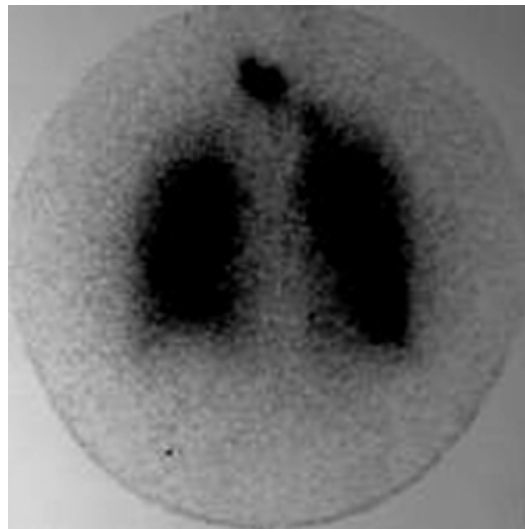


FIG. 9.1 (c). Post-surgical low dose WBS revealing pulmonary metastasis (looks like perfusion lung scan).

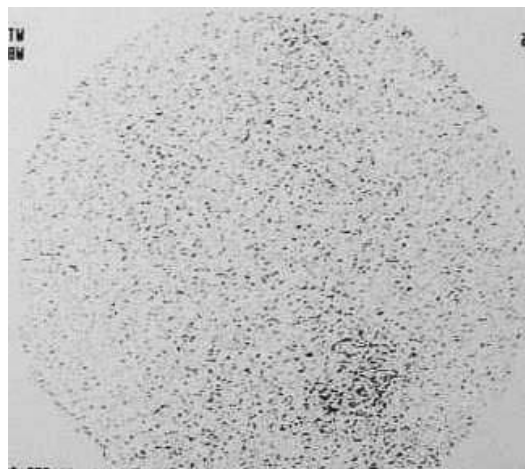


FIG. 9.1 (d). Post-therapy WBS showing no ^{131}I concentration in the lungs.

Summary of Figs 9.1(a)-(d): a — Chest X Ray Post-surgical low-dose ^{131}I WBS revealing pulmonary metastasis) b — High resolution CT scan. c — Post-surgical low-dose ^{131}I WBS revealing pulmonary metastasis (looks like perfusion lung scan) d — Post-therapy WBS showing no ^{131}I concentration in the lungs

9.9.4. Tumour response to radioiodine therapy and possible adverse effect

Overall, the radioiodine therapy in children is effective and gives long term disease-free survival. However, none of the independent co-variables like sex, histopathology, ^{131}I uptake, administered and absorbed dose appears to have any influence over the dependent variable (ablation) [9.28]. It seems that there is one elusive factor which affects radioiodine ablation of thyroid tissue. Probably it is 'radiosensitivity of thyroid tissue'. This biological variable is unknown, undefined and unpredictable and currently unmeasurable. One of the possible adverse effects of treatment with ^{131}I , especially in children, is its effect on the gonads. For further details, please refer to the Chapter "Long term Follow-up Strategies".

9.10. External radiotherapy

External radiation plays a minor role in the management of childhood thyroid cancer. It is useful in special situations where either the primary tumour is inoperable or there is an extensive invasive disease with soft tissue, tracheal or oesophageal infiltration. The outcome of the treatment is usually unsatisfactory and the post-therapy complications are frequent and severe.

9.11. Follow-up

Optimum follow-up protocol should be as follows: Post-surgical ^{131}I WBS should be performed with 74-111 MBq (2-3 mCi) of ^{131}I along with 48-hour radioiodine uptake (RAIU) after keeping patients off L-thyroxine for 4-6 weeks. If radioiodine therapy is planned, the dose of ^{131}I should be decided on the basis of RAIU in cases of remnant thyroid tissue, and spread of disease in cases of distant metastases. The patients should then be advised to take TSH-suppression therapy consisting of 0.2-0.3 $\mu\text{g}/\text{kg}$ of L-thyroxine daily on empty stomach. Six months later a diagnostic WBS is performed as described above together with Tg assay. Criteria for not ablating include: a) negative ^{131}I WBS, b) 48-hour RAIU $\leq 0.2\%$ and/or c) Tg ≤ 10 ng/ml [9.65]. Radioiodine therapy can be repeated annually until ablation is achieved. Thereafter, the patients can be followed with yearly clinical examination, chest X ray and Tg determination. If disease-free, then 5-yearly ^{131}I WBS is advised and the patient is followed up indefinitely.

9.12. Mortality

The overall mortality rate reported in the literature varies from 0-18%. An increase in the incidence of DTC in children and a decline in the mortality rate has been reported [9.54, 9.66]. The reported respective 5-year, 10-year, 15-year, and 20-year survival is 90-95% [9.16], 86-94% [9.67], 75-98%, [9.6, 9.15] and 82-96% [9.12, 9.16, 9.17]. However, in one study, the 20-year survival rate for PTC has been 100% [9.16]. Despite the aggressive nature of thyroid carcinoma in children, the outcome and long term survival is very good. Although rare, occasional mortalities do occur especially in children who are less than 10 years old at the time of diagnosis.

9.13. Prognostic factors

The host and tumour factors are predictor of survival in almost all cancers. There is some peculiarity in DTC, more so in paediatric DTC. None of the known variables like age, sex, histology, type of surgery, radioiodine therapy and nodal status influences survival. However, different series have stressed on different variables. This is because very few large series have been published with long term follow-up. Although a multivariate analysis is an appropriate method to determine the importance of prognostic factors for cancer outcome, only a few such studies have been performed owing to the rarity of DTC in children [9.18, 9.68-9.75]. In most of the published report the number of children is too small, and the upper age cut-off varies from 12-year to 25-years that does not permit robust statistical analysis.

Most of the studies demonstrate good prognosis for thyroid cancer in children. However, to determine death rate, the duration of follow-up should be longer than 5 years in the majority of patients. Schlumberger, et al. [9.17] showed that 6 out of 72 children with DTC died 12-33 years after initial treatment. On the other hand, it is well known that the vast majority of recurrences occur in the first 5 years after the primary treatment. Therefore the importance of prognostic factors is calculated in relation to disease-free survival.

There is disagreement in the literature on the relation between tumour histopathology and disease free survival. While La Quaglia, et al. [9.18] noted fewer relapses in follicular cancer, others have shown a better prognosis for papillary tumours [9.76-9.77]. In this series, there was no correlation between tumour histopathology and disease-free survival, although the patients with follicular cancer were quite numerous. This is probably due to the moderate iodine deficiency which was observed in Northern India till mid eighties [9.28].

For a long time lymph node metastases were not considered a negative prognostic factor in DTC [9.8, 9.21, 9.78-9.81]. Recently, more and more authors have claimed that local metastases adversely influence disease-free survival [9.21, 9.82-9.84]. Mazzaferri and Jhiang [9.21] showed an increased risk of relapse in young patients with lymph node metastases without any influence on overall survival. Similar observations were described by De Groot, et al. [9.82] and Salvesen, et al. [9.83]. Robie, et al. [9.84], in their univariate analysis, noted a strong trend toward locoregional recurrence with a higher number of pathologically positive lymph nodes (more than four). Jarzab, et al. [9.29] observed a significant negative effect in their analysis of a combined group of children and young adults. In this group, diagnosis of lymph node metastases was associated with a doubled risk of recurrence.

Patient age at diagnosis is a well known factor influencing relapse rate [9.21, 9.85]. Most studies, however, include both children and adults. Mazzaferri, et al. [9.21] noted the highest rate of recurrences in patients younger than 10 or older than 60 years. Similarly, the report from the children's Cancer Study Group [9.75] had claimed that the younger the child at diagnosis, the higher the rate of relapse.

In the literature there is much controversy over the influence of sex on disease free survival in DTC. Schlumberger, et al. [9.17] and Jarzab, et al. [9.29] found no influence of a child's sex on disease free survival. By contrast, others [9.21, 9.83] have reported that the rate of relapse is higher in males. Farahati, et al. [9.75] noted a trend toward more metastases in males with a borderline significance.

Although all unequivocally agree that surgery should be the initial treatment for DTC, the optimal extent of surgery is debated, especially in children. Zimmermann, et al. [9.6],

Desjardins, et al. [9.3] and La Quaglia, et al. [9.18] opt for a conservative surgical approach, despite the fact that they showed a high rate of recurrence in their non-radically operated patients. No impact of surgical management on the outcome in children with DTC was found in two recent statistical analyses [9.68, 9.82]. Robie, et al. [9.84] advocated total or subtotal thyroidectomy only if adjuvant radioiodine therapy was planned. Routine use of radical thyroid surgery in their study did not improve the outcome and was associated with an increased risk of complications. In their opinion complete thyroid removal should be standard in patients with distant metastases, extensive lymph node involvement or invasive extracapsular tumours.

Newman, et al. [9.68] in a multicentre study, showed no difference in progression-free survival between children undergoing lobectomy or even less extensive surgery and those treated by total or subtotal thyroidectomy. They stressed only the significance of controlling for residual cervical disease. However, Jarzab's [9.29] results are in strong opposition to this. Their recurrence rate (15%), which is lower than Newman's rate of 30%, showed a distinct relation to the extent of surgery. Of those patients who underwent less than total thyroidectomy, only 15% remained relapse free after 10 years, with 59% of them having relapsed during the first 5 years of observation. By contrast, disease-free survival was very good in patients treated by total thyroidectomy.

There is a risk of bias in the estimation of the recurrence rate following surgery performed at many centres over a long period of time, as disease free patients may more easily disappear from the long term control. Whereas some authors question the necessity of extensive thyroid surgery, others [9.20, 9.29, 9.48, 9.86] accept radical surgery, followed by radioiodine treatment, as the most adequate. In their opinion, combined treatment decreases the rate of local and distant metastases.

Mazzaferrri, et al. [9.21] and Samaan, et al. [9.77] showed clearly the therapeutic benefit of ^{131}I as complementary treatment for DTC, This effect was observed not only in adults but also in children and regardless of whether the risk of recurrence was low or high. In fact, radioiodine treatment results not only in thyroid ablation but also in the treatment of micrometastases undetectable by other imaging method [9.49]. This is why it improves the disease free survival. Various authors have estimated the prevalence of micrometastases at 17-56%. In this experience as also [9.28], 75% of patients with pulmonary metastases had normal chest X rays and in 35% patients even high resolution CT scans were negative. Pulmonary metastases were detected in post-surgical low dose ^{131}I WBS or post-therapy scans (scans done after administration of large dose of ^{131}I). These patients were mostly asymptomatic and pulmonary metastases would have remained undetected for a longer time, increasing morbidity and mortality significantly, if remnant thyroid tissue ablation with radioiodine were not attempted in these patients. Furthermore, these patients responded very well to ^{131}I therapy.

9.14. Conclusion

Differentiated thyroid cancer in children is rare. The biological behaviour differs from that in adults and is related to the factor of age. Younger the age (<10 years), more aggressive and widespread is the disease with male preponderance and high mortality. Response to ^{131}I therapy is excellent. A total/near total thyroidectomy followed by ^{131}I ablation of residual/remnant thyroid tissue and nodal or distal metastases if present reduces the rate of mortality and recurrence.

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10. SURGICAL MANAGEMENT

10.1. Introduction

In 952 A.D. a Moorish physician named Albucasis performed the first successful thyroidectomy. Unfortunately, his work was largely forgotten, and for many hundreds of years there was no progress in thyroid surgery. In fact in 1850, the mortality rate for thyroid surgery was very high, about 50% of patients died following thyroidectomy, usually from uncontrolled bleeding. Theodor Kocher of Berne, Switzerland made outstanding contributions to the understanding of thyroid disease at the turn of the past century. By 1901, he had performed 2000 thyroid operations [10.1]. In recognition of his accomplishment, he was awarded the Nobel Prize in Medicine in 1909. Since that time, there have been major advances in the understanding of thyroid disorders and in the management of patients with thyroid nodules. During the 1940's and 1950's, attempts were initiated to develop criteria for different operations for the thyroid nodules and determine the frequency of thyroid carcinomas. Thyroid scans using radioactive iodine became available and were frequently used in identifying functional abnormalities of the thyroid gland. However, it soon became evident that this procedure was of little help in separating malignant from the more numerous benign thyroid nodules.

10.2. Pre-operative evaluation

Pre-operative preparation of patients for thyroidectomy may include evaluation of thyroid function and vocal cord movement by direct or indirect laryngoscopy. Ultrasonography is done to find thyroid nodules and regional lymph nodes. Determination of urinary catecholamines, metanephrine, and vanilylmandelic acid (VMA) are done in patients suspected of having medullary thyroid carcinoma and to rule out possible co-existent pheochromocytoma. Serum calcium determination is done to look for primary hyperparathyroidism.

Thyroid fine needle aspiration biopsy (FNAB) is a non-surgical diagnostic procedure which can differentiate malignant and benign nodules of the thyroid in most cases. The cytology report usually is classified as non-diagnostic, benign, suspicious or malignant. Non-diagnostic cytology indicates that there is insufficient number of thyroid cells in the aspirate. Aspiration should be repeated since a diagnosis will be obtained in approximately 50 per cent of the repeat aspirates. Benign thyroid aspirations are the most common. They consist of benign follicular epithelium with a variable amount of colloid. Malignant thyroid aspirations may include cytology findings consistent with thyroid cancer which may be papillary, medullary, anaplastic and thyroid lymphomas. Follicular thyroid carcinoma (FTC), follicular variant of papillary, Hurthle cell carcinoma, and follicular adenoma can not be differentiated by FNAB. These patients often end up requiring surgical removal of the thyroid lobe that harbours the nodule. Suspicious cytology reports make up approximately 10 per cent of FNABs. Surgery is recommended for the treatment of thyroid nodules from which a suspicious aspiration has been obtained.

According to Aversa, et al., [10.2] FNAB, which has a diagnostic accuracy of 88.3% (Sensitivity 85.7% and Specificity 89.3%), is still the most reliable technique for the diagnosis of thyroid neoplasms.

10.3. Thyroid surgery

An incision that provides a clear exposure of the thyroid gland, maintenance of a relatively bloodless field, and appropriate traction and counter traction of the thyroid gland, all aid in the performance of a safe operation. Thyroid surgery is performed with the patient in supine position with a hyperextended neck. A rolled towel is placed under the shoulders for better neck exposure. A low transverse cervical incision is made two finger-breadths above the manubrium. An incision made too low results in a scar that is much more conspicuous if it descends down to the level of the manubrium when the neck is no longer hyperextended. The lateral borders of the incision approach the medial borders of the sternocleidomastoid muscle but can be lengthened if the lateral neck is to be investigated. Subplatysmal flaps are created both cephalad and caudad. The midline raphe is opened and the lobe with the tumour is exposed after separating the sternothyroid muscles off the thyroid capsule. Lobectomy is initiated by mobilizing the supero-medial aspect of the thyroid, which is tethered to the larynx by the suspensory ligament. A small vessel in the suspensory ligament is ligated. The superior thyroid vessels are skeletonized, ligated, and divided. The superior branch of the external laryngeal nerve is usually located superior to the superior thyroid vessels. It should be identified and protected. Next, the middle thyroid vein is placed on traction, doubly ligated, and divided. The recurrent laryngeal nerve is in the tracheoesophageal groove and visualization of this nerve is of utmost importance. The nerve should be sought, visualized and protected. The dissection is aided if the lobe of the thyroid is rotated medially and anteriorly by finger traction on a gauze sponge.

The surgeon preserves the blood flow to the parathyroid glands by ligating the inferior thyroid artery close the thyroid gland [10.3]. Occasionally in some cases, the blood flow to the parathyroid gland could not be preserved. The glands should be removed and placed in a sterile iced saline solution. A small portion is sent for frozen section and if it is confirmed to be parathyroid tissue, the gland is sliced into small fragments and transplanted to the sternocleidomastoid muscle. The isthmus is dissected from the trachea. Lobectomy and isthmectomy are completed with full visualization of the recurrent laryngeal nerve and parathyroid glands. Particular care must be taken near the cornu of the larynx just before the nerve enters the larynx. A remnant of less than 2 grams, sufficient only to preserve the parathyroid glands, should be left in place.

The use of modified radical neck dissection in differentiated thyroid cancer (DTC) is primarily reserved for patients with clinically palpable cervical lymph node metastases [10.4, 10.5]. There is limited literature on the efficacy of prophylactic neck dissection in patients with well-differentiated thyroid carcinoma who do not have palpable lymph nodes [10.6]. In patients with papillary thyroid carcinoma (PTC), concern about multicentric foci in the remaining thyroid gland and microscopic lymph node involvement fuels this controversy. Radioactive iodine appears to be beneficial in such circumstances, but it is much less effective in ablating palpable regional metastatic lymph nodes. The use of selective removal of palpable nodes in the lateral compartment (Berry/cherry picking) has largely been abandoned. Modified radical neck dissection can be accomplished using an enbloc dissection that removes all of the lymphatic and adipose tissue in the lateral neck compartment while avoiding the cosmetic or functional abnormality of removal of muscle groups employed in the classic radical neck dissection. The sternocleidomastoid muscle and spinal accessory nerve are spared if possible. When enlarged lymph nodes are present either in the tracheoesophageal groove, the superior mediastinum, or the jugular area, central compartment clearance should be done. Staging and score systems may be helpful in calculating prognosis in DTC. The

benefit of systematic lymphadenectomy, in all cases, remains controversial [10.7]. At the conclusion of the operation, the operative field is checked for bleeding. The platysma is approximated with fine interrupted absorbable sutures. A drain is optional. But if used, it is placed in the thyroid bed and the other end is brought out through a gap in the middle of the incision and sutured in place. The skin incision is closed with a fine interrupted or continuous suture.

10.4. Risk groups in differentiated thyroid cancer

A good understanding of the risk groups in DTC is important before the extent of thyroid surgery can be determined. There are several prognostic factors that were studied using univariate and multivariate analysis in the past three decades. The first study was done by the European Organization for Research and Treatment of Cancer (EORTC) Thyroid Cancer Group [10.8]. Other similar studies came from the Mayo Clinic, [10.9] the Lahey Clinic, [10.10] and Memorial Sloan-Kettering Cancer Centre [10.11]. The major prognostic factors in all of these studies were patient's age, tumour grade, distant metastasis, tumour size and extra-thyroidal extension. The scheme for categorizing patients with well-differentiated thyroid cancer by prognostic risk categories is shown in Table 10.1 [10.12].

According to Dean and Hay [10.13] the most important prognostic factor in the evaluation of thyroid cancer patients are the age of the patients, tumour grade, distant metastasis, extra-thyroidal extension, tumour size, and completeness of resection. Based on their evaluation, patients are divided into low-risk and high-risk groups. Survival rate is higher in the low-risk group. Lymph node metastasis at the time of initial examination seems to have little influence on the risk of death from papillary thyroid carcinoma. However, it increases the risk of loco-regional recurrence and decreases the survival rates of follicular thyroid carcinoma. Poorly differentiated tumours are often locally invasive and are associated with a much worse prognosis.

Shah and colleagues [10.11] at the Memorial Sloan-Kettering Cancer Centre analysed the different prognosticators of thyroid cancer based on patient-related and tumour related factors. They divided the patients into low, intermediate, or high-risk groups. The high-risk tumours are those with any of the following characteristics: follicular histology, extra-thyroidal extension, tumour size exceeding 4 cm, and presence of distant metastases. Patients who are less than 45 years old are low-risk while those over 45 years old are high-risk patients. The low-risk group consisted of low-risk patients (under age 45) with low-risk tumour, and the high-risk group consisted of high-risk patients (above the age of 45) with high-risk tumour. The intermediate-risk group consisted of low-risk patients (under the age of 45) with high-risk tumour or high-risk patients with low-risk tumour. Based on these separate risk group categories, these investigators had determined significant differences in their survival rate (low-risk= 99%, intermediate-risk= 87%, and high-risk= 57%) at 20 years).

The appropriate surgery of thyroid cancer patients should be based on the risk-group analysis. In the low-risk group, lobectomy (hemithyroidectomy) are probably sufficient. In the intermediate-risk group, the extent of surgery should be based mainly on tumour-related factors. If RAI therapy is needed to eradicate the residual thyroid tissue, total thyroidectomy should be done to decrease the RAI dosage. Beenken, et al. [10.14] encourage total thyroidectomy for all intermediate-risk patients with DTC since they believe that it provides a higher survival advantage. Patients in the high-risk groups should undergo total thyroidectomy [10.15].

TABLE 10.1. COMMON PROGNOSTIC RISK CATEGORIES FOR PATIENTS WITH WELL-DIFFERENTIATED THYROID CANCER [10.12]

	Low Risk	Intermediate Risk	High Risk
AMES			
Age	Males <41 y, female <51 y		Male >40 y, female >50 y
Metastases	No distant metastases		Distant metastases
Extent	Intra-thyroidal papillary or follicular with minor capsular invasion		Extra-thyroidal papillary or follicular with major invasion
Size	<5 cm		>5 cm
Definition	A: Any low-risk age group without metastases B: High-risk age without metastases and with low-risk extent and size		A: Any patient with metastases B: High-risk age with either high-risk extent or size
DAMES			
Definition	Low-risk AMES + euploid	Low-risk AMES + aneuploid	High-risk AMES + aneuploid
AGES			
Prognostic Score= $0.05 \times \text{age in years (except patient } <40 \text{ y} = 0)$, + 1 (grade 2) or + 3 (grade 3-4), + 1 (if extra-thyroidal) or + 3 (if distant metastases), + $0.2 \times \text{tumour size (in centimetres, maximum diameter)}$			
PS range: 0-11.65; median 2.6			
Risk Categories: 0-3.99; 4-4.99, 5-5.99; >6			
MACIS			
Prognostic Score= 3.1 (age <39 y) or $0.08 \times \text{age (if age } >40 \text{ y)}$, + $0.3 \times \text{tumour size (in centimetres)}$, + 1 (if incompletely resected), + 1 (if locally invasive), + 3 (if distant metastases)			
Risk categories: 0-5.99; 6-6.99; 7-7.99; >8			

10.5. Surgical management of differentiated thyroid cancers: total vs. near total thyroidectomy

Papillary thyroid cancer and follicular thyroid cancer are both well-differentiated thyroid cancers. All types of papillary, follicular, and follicular variant of papillary cancers account for 90% of all cases. PTC is the most common of the thyroid neoplasms occurring in 80% of thyroid cancer in iodine sufficient areas. It is usually associated with an excellent prognosis. Data from the National Cancer Data Bureau of the U.S. reported that patients with stage I, II, and III localized to the neck have similar 5-year survival of about 90%. However, patients who present with distant metastasis (Stage IV), primarily to the lungs have significantly decreased 5-year survival of 50%. Other reports have similar data with 10-year survival rates for all patients with early stage PTC in the range of 80% to 90%. FTC incidence is dependent on environmental iodine status, constitutes 10% of the thyroid malignancies in iodine sufficient areas and much higher in iodine deficiency endemias. The 10-year survival for patients with FTC is approximately 75-80%. This is significantly less than patients with PTC. The 5-year survival for stage III and IV FTC is 70% and 40%, respectively.

Proponents of the ‘near total thyroidectomy’ argue that there is insignificant decrease of local recurrence and mortality following total thyroidectomy, to justify the potential risks of recurrent laryngeal nerve injury and permanent hypoparathyroidism. They argue that the reported incidence of recurrent nerve injury (0-7%) and permanent hypoparathyroidism (0-8%) varies with the extent of operation, the history of previous neck surgery, and the

experience and training of the surgeons [10.16-10.19]. Brooks and colleagues treated 222 patients of DTC, with total thyroidectomy (43 patients) or near total thyroidectomy (179 patients) and found no difference in recurrence or survival rate (21). Shah, et al. concluded in their retrospective study that low risk patients (primary tumour of 4 cm or less, limited to the thyroid gland, without gross contralateral disease, and no evidence of distant metastasis) who underwent total thyroidectomy had no survival advantage over lobectomy. They also feel that the cervical lymph node metastasis may have a minor effect on local recurrence in high-risk patients who are over 45 years old. In the low-risk patients, the presence or absence of nodal metastasis has no effect on long term survival (22). Some believe that patients with occult PTC (less than 1 cm) or FTC with minimal capsular invasion can be treated with thyroid lobectomy and isthmectomy only because the long term survival approaches 100% (23-26). For low-risk DTC patients, lobectomy is adequate (27-30). Other investigators also believe that the extent of lymphadenectomy, partial or total thyroidectomy does not influence survival in most patients with DTC [10.7, 10.28-10.27].

Advocates of 'total thyroidectomy', on the other hand, argue that complete removal of the thyroid gland may provide a survival advantage for intermediate risk patients with DTC [10.14]. Soh and Clark [10.25] enumerated the following reasons for doing a total thyroidectomy: (1) in patients with papillary carcinoma, intraglandular tumours occur in the opposite lobe in 30% to 87.5% of patients; (2) recurrent thyroid carcinoma develops in the contralateral lobe in 75-100% of patients if followed long enough; (3) approximately half of all patients with recurrent thyroid carcinoma die of the disease; (4) virtually all studies show lower recurrence and better long term survival in patients who underwent more aggressive initial treatments; (5) total thyroidectomy removes all normal thyroid tissue that will facilitate earlier detection and treatment of recurrent or metastatic carcinoma with RAI; (6) serum thyroglobulin determination is more sensitive and accurate in detecting tumour persistence and recurrence in patients who undergo total thyroidectomy; (7) total thyroidectomy reduces the small chance that a differentiated tumour might degenerate to an anaplastic carcinoma (ATC); and (8) in experienced hands, total thyroidectomy can be accomplished with a negligible mortality and with complication rates less than 3%. Santini and others recommend total thyroidectomy as a safe treatment for DTC, because of its low morbidity rates, in the hands of experienced surgeons [10.26-10.28].

It is generally agreed that total thyroidectomy in DTC is the treatment of choice for the following cases: patients with >4 cm tumours, gross disease in both lobes, poorly differentiated tumour, thyroid cancer in patients with a history of radiation, young patients with bulky nodal disease requiring lymph node clearance, and presence of distant metastasis requiring post operative RAI ablation [10.29]. The fact that local recurrence signifies a substantial risk of subsequent tumour-related mortality should be emphasized. Total thyroidectomy eliminates the multi-centric microscopic foci present in up to 85% of PTC as potential sites of local recurrence, or the anaplastic transformation that occurs in 1%. Patients undergoing lobectomy have a recurrence rate in the contralateral lobe of 5 to 25%, with a mean of 7%. Up to one-half of the patients who were initially considered as 'low-risk' eventually died of thyroid cancer. Tollefsen, et al. reported a 5.7% local recurrence rate in the contralateral thyroid remnant, and 41% of these patients died. Mazzaferri and Young [10.31] reported a recurrence rate of 11% after total thyroidectomy compared with 22% after subtotal thyroidectomy. The result of these retrospective studies probably underestimates the benefits of these treatments because patients with more extensive disease were more likely to be included in the group receiving more extensive treatment.

The Mayo Clinic experience [10.9] showed that in both low-risk (AGES score 3.99 or less) and high risk (AGES score of 4 or more) groups, there was a highly significant difference in the risk of local recurrence, comparing unilateral and bilateral resections. Seiler and colleagues [10.32] consider total thyroidectomy and modified neck dissection as the standard operation in DTC. In unilateral carcinoma both the central and the ipsilateral cervico-lateral lymph nodes should be dissected. The authors performed bilateral cervico-central and cervico-lateral lymphadenectomy in multicentric bilateral carcinomas. If only a unilateral lobectomy has been performed initially for a follicular cell-derived cancer, it is often prudent to consider completion thyroidectomy for lesions that are anticipated to have an aggressive behaviour, because large thyroid remnants are difficult to ablate with radioactive iodine [10.33]. Radioiodine remnant ablation has often been used after near-total or total thyroidectomy to 'complete' initial therapy in follicular cell-derived cancer, but it should be used selectively [10.34]. Ablation is not recommended for low-risk PTC cases (with AGES scores <4 or MACIS scores <6), but it is regularly employed as post-operative therapy in patients with FTC (including the oxyphilic variant tumours) or high risk PTC patients with MACIS scores of 6 or more [10.13].

It should be noted that even in the early 21st century, there continues to be a lack of international consensus regarding the extent of initial surgery and whether radioactive iodine should be routinely administered for postoperative remnant ablation [10.35].

10.6. Medullary thyroid cancer

Medullary thyroid carcinoma (MTC) accounts for approximately 5% of all thyroid carcinomas [10.36, 10.37]. MTC can occur in association with familial cancer syndromes (MEN-2A, MEN-2B, and familial MTC), and family members should be screened for the presence of ret mutations [10.38]. Total thyroidectomy at a young age in patients who have the mutation before the development of carcinoma can be performed safely and will likely cure patients of an otherwise incurable disease [10.39]. Patients with MTC should also be screened for pheochromocytoma because this tumour occurs in approximately 40% of MEN-2 patients [10.40]. Patients with pheochromocytoma should undergo adrenalectomy first, although combination procedures have been described with excellent results.

Treatment for MTC is total thyroidectomy, with appropriate central compartment clearance, including removal of the paratracheal nodes, the tracheoesophageal groove nodes, the nodes around the internal jugular vein, and the superior mediastinal nodes. The estimation of calcitonin, a tumour marker, permits detection and postoperative monitoring of MTC patients. It is important to identify whether MTC belongs to sporadic or hereditary category. In the sporadic MTC, total thyroidectomy is the preferred operation because it is not always possible to eliminate the possibility that the tumour is of hereditary variety which is uniformly bilateral. The occurrence of cervical lymph node metastasis and the aggressive nature of this carcinoma justify concomitant central, upper mediastinum and lateral cervical lymph node dissection [10.41, 10.42]. The classical lateral cervical lymph node dissection is done in patients with palpable and locally invasive metastases; but it is modified for patients who do not exhibit palpable lymphadenopathy. Familial MTC is treated by total thyroidectomy as it involves both lobes of the gland. Survival of patients following surgery is dependent on the extent of the disease. In general, patients without lymph node metastases (stage I and II) are cured by total thyroidectomy. However, survival is significantly reduced as the stage of the disease progresses, with stage III disease having a 4-year survival of 80% and stage IV disease having a 5-year survival of 40%.

10.7. Anaplastic cancer

ATC represents less than 1% of all thyroid malignancies. It is the most aggressive form of thyroid cancer. The major problem with ATC is that it is usually too aggressive and invasive when it is diagnosed. Therefore, only a small number of patients can undergo surgical resection of the cancer. Total thyroidectomy is the preferred treatment for operable disease. A typical presentation is dysphagia, cervical tenderness, and a painful neck mass in an older patient. Superior vena cava syndrome can also be a part of the presentation. The clinical situation deteriorates rapidly into tracheal obstruction and rapid local invasion of surrounding structures. The goal of surgical treatment is to maintain a patent airway and, if possible, clear the neck of disease. Surgery has a limited role in the primary treatment. Once the diagnosis is established, patients should be treated with hyperfractionated radiotherapy and doxorubicin-based chemotherapy [10.42]. The finding of distant metastasis or invasion into locally unresectable structures, such as the trachea or vasculature of the anterior mediastinum, should lead to a more conservative surgical approach, such as tracheostomy. ATC has the worst prognosis of all thyroid malignancies, with a median survival of about 18 months and 5-year survival rates of approximately 10% [10.44].

10.8. Postoperative complications

Bleeding in the neck with compromise of the airway is the most dangerous complication of thyroidectomy. In the patient with laboured or stridorous respiration, rapid removal of skin, platysma and strap muscle sutures is essential at the bedside or in the operating room (if time permits) to decompress the neck haematoma.

Transient hypocalcemia occurs in approximately 10 to 15% of patients who undergo bilobar thyroidectomy, and serum calcium levels should be monitored every 6 hours starting 6 hours after operation and stopping at 24 hours if all levels have been normal. If serum calcium levels drop below 7.0 mg/dl or if the patient is symptomatic, intravenous calcium gluconate is administered and oral calcium supplements are begun. Permanent hypocalcemia can be treated with chronic oral calcium and vitamin D supplementation.

Recurrent laryngeal nerve injury is usually the result of a stretch or contusion of the nerve, and recovery may be appreciated in 3-6 months. There are some instances when intentional resection of the nerve for enbloc clearance of variant papillary, Hurthle cell, MTC or ATC is done. Involvement of the nerve by most PTC or FTC is best treated if possible by 'shaving' tumour from the nerve with expectation that radioiodine therapy will ablate residual carcinoma. If bilateral recurrent nerve injury was encountered, dangerous airway occlusion may be seen and this requires immediate tracheostomy.

Damage to the superior laryngeal nerve may cause additional difficulty. The superior laryngeal nerves are responsible for adduction of the cords and also supply innervation to the larynx and pyriform sinus. Loss of sensation in this area can increase the chance of aspiration. Vocal cord paralysis can also be a complication of general anaesthesia and endotracheal intubation.

10.9. Postoperative treatment

Multidisciplinary approach and intense planning among the surgeon, endocrinologist, and nuclear medicine specialist achieve the best postoperative management of thyroid cancer patients.

For low risk patients of PTC, thyroid suppression is begun immediately postoperatively with an intention to keep TSH levels in a range of 0.1 to 0.4 mIU/L. No radioiodine therapy or scan is required. Follow-up consists of biannual physical examination of the neck. Intermediate and high risk patients with DTC who underwent total or near-total thyroidectomy are given thyroid hormones (T3) for 3 weeks which is then discontinued for 3 weeks until TSH levels are greater than 30 mIU/L. They are then seen by a nuclear medicine physician for radioiodine ablation therapy. Seven to 10 days after the RAI therapy dose administration, whole-body scanning is done to determine presence of metastasis. Diagnostic scanning can be repeated after 12 months to document any residual uptake that may require a repeat high-dose ablation. In few patients with highly aggressive disease, the scanning can be repeated after 6 months. All patients who undergo surgery and remnant ablation receive thyroid hormones indefinitely to suppress TSH levels below 0.1 mIU/L. They are monitored by biannual neck examinations and serum thyroglobulin determinations. Radioiodine whole-body scan to detect any recurrence should be done in patients whose serum thyroglobulin levels rise above 5ng/ml during suppressive thyroid replacement or above 10 ng/ml when hypothyroid. Lymph node recurrences should be treated by local excisions. Bone metastasis resistant to radioiodine may be treated by localized radiotherapy for palliation.

Patients with MTC will also require thyroid hormone replacement. However, rigorous suppression of TSH levels is not correlated with outcome. Measurement of serum calcitonin levels is performed at 3-month intervals for the first 3 years after operation and biannually thereafter. Postoperatively, plasma levels of calcitonin can be used as a marker to detect recurrent disease. Elevated basal or pentagastrin-calcium stimulated levels of calcitonin are signs of recurrent MTC. Some calcitonin-suspected MTC recurrences can be localized by neck ultrasound, MRI, CT, or by nuclear medicine scans. Whole body somatostatin (octreotide) scanning may be more useful in these patients. Prior to reoperation, venous sampling for calcitonin should be used to indicate which side of the neck has disease. Laparoscopy of the liver may be considered to exclude small liver metastases that may be present and undetectable on imaging studies. Repeated surgical excision of MTC recurrences should be performed if feasible. Genetic investigation of the patient's relatives for heritable MTC is an ethical responsibility of the treating physician, especially if the presence of multicentricity, bilateral MTC, or diffuse C-cell hyperplasia suggests a familial aetiology.

Patients with ATC should undergo monthly follow-up to monitor for palpable recurrence or complications that require additional therapy. Resection of recurrent tumour may be helpful occasionally but is rarely feasible technically.

10.10. Summary

Determining the extent of thyroidectomy in the management of DTC is controversial. The principal reason of this controversy is the fact that the majority of patients with DTC do extremely well with patients surviving for decades. When near total or total thyroidectomy can be done with minimal complications, it is believed that this is the treatment of choice for most thyroid cancers.

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11. RADIOIODINE THERAPY

Radioiodine (^{131}I) therapy has been introduced for the treatment of thyroid diseases since 1946 by Seidlin, et al. [11.1]. The use of radioiodine in the treatment of functioning distant metastases has been well accepted, however, its use in remnant ablation for well-differentiated thyroid cancer is still controversial [11.2, 11.3]. As the incidence of the disease is very low and the nature of the malignancy is indolent, a large number of cases to establish good statistical data are required. Most published reports deal with a small series of cases and hence are not statistically significant. In order to overcome these deficiencies, reports are now being published on collated data obtained from several centres [11.4]. Here again the problems encountered are the differing protocols for treatment with radioiodine, the indications for treatment which may include or exclude ablation of residual thyroid tissue, cervical nodal metastases and distal metastases. The doses of radioiodine given for ablation of residual thyroid tissue and metastatic disease also vary. The most reliable conclusions regarding treatment protocol encountered in radioiodine treatment are obtained from retrospective studies reported on a large series of patients followed over a period of several decades from single institutions with a more or less unchanged protocol of treatment. Such studies are few. These reports from a handful of centres around the world are the most referred and cited studies [11.5-11.8].

The use of ^{131}I has continued as a mainstay of therapy for thyroid cancer today. The growing awareness of subtle short- and long term consequences of this therapy and its ineffectiveness in advanced metastatic thyroid carcinoma have led to a more cautious and conservative approach to its use. This review is intended to highlight the areas in which ^{131}I therapy has had its greatest achievements as well as those clinical situations in which its use is not supported by clinical experience or retrospective studies.

11.1. Postoperative management of primary thyroid carcinoma

Four to five weeks after surgery and without supplementation of thyroxine, all patients undergo a diagnostic study with 111-185 MBq (3-5 mCi) of ^{131}I to assess the amount of residual or remnant thyroid tissue. If the radioiodine uptake is above 15% and a neck scan shows a significant amount of thyroid remnant tissue then a revision or completion thyroidectomy may be considered. Those patients who have large palpable nodes in the neck which may have been noticed after the primary thyroidectomy are advised nodal clearance. Following revision surgery, another diagnostic radioiodine scan and uptake study is undertaken which will determine the necessity of radioiodine treatment. Surgery of the primary thyroid is performed in many small hospitals all over the country and as a result of the lack of adequate experience and confidence of the surgeons the extent of the thyroid removal ranges from a nodulectomy to a subtotal thyroidectomy to a near total thyroidectomy. Hence the need for diagnostic large dose radioiodine for the further management is indicated.

At the centre, patients are given radioiodine therapy depending on the neck uptake and extent of metastases as evident from whole body scan findings. Those patients who show very low neck ^{131}I uptakes (<0.1%), little or no concentration on a neck scan and undetectable levels of serum thyroglobulin, are declared surgically ablated. Such patients are not treated with radioiodine and are started on thyroxine suppression. All those patients with scan evidence of remnant thyroid and uptake >0.1% are given therapy for the ablation of the residual thyroid.

11.2. Diagnostic radioiodine studies

11.2.1. Pre-ablation studies following surgery

Increasing radioiodine uptake by remnant thyroid tissue

In order to increase the uptake of radioiodine by the residual thyroid and/or microscopic metastases diagnostic test should be done under a maximally elevated serum TSH. After surgical removal of the thyroid, the TSH starts rising by 2 weeks and by 4-6 weeks is maximally elevated. This results in a higher uptake and better chance for successful ablation of the thyroid with ^{131}I therapy. The time course of TSH elevation is different from patient to patient probably because of the variable metabolism of circulating and stored T₄. However 6-8 weeks is sufficient for over 90% of patients to show elevated TSH value.

In the analysis, the ablation of residual tissue was better when the TSH levels were more than 30 $\mu\text{IU/ml}$. This observation is supported by reports indicating that adequate stimulation by TSH is an essential prerequisite for complete ablation [11.9]. Hence, post-surgery, T₄ is not administered and diagnostic studies are performed 4-6 weeks after the surgery.

Depletion of stable iodide concentration

An attempt should be made to reduce plasma inorganic iodine concentration in the body particularly in iodine sufficient countries. Patients are instructed to avoid all iodine containing substances for 4-6 weeks prior to the test. Since stable and radioactive iodine compete at the level of the iodide trap, an increase in concentration of serum inorganic iodine results in a lower uptake of radioiodine whereas a decrease results in a higher uptake. Morris, et al. [11.10] from California re-evaluated the impact of a stringent low-iodine diet on ablation rates in radioiodine treatment of thyroid carcinoma. The group retrospectively reviewed first-time, short-term ablation rates for 44 low-iodine diet (LID) patients and 50 patients following a regular diet (RD) who were verbally instructed to avoid salt, seafood, and multivitamins containing iodine. Patients who had undergone ablation were given between 3700MBq and 7400MBq (100 and 200 mCi) of ^{131}I , depending on the presence of metastases. They observed a 68.2% ablation rate for LID patients, compared to a 62.0% rate for RD patients, a nonsignificant difference ($p= 0.53$). Interestingly, they have noted a dose-response relationship for both patient groups, with higher ablation rates corresponding to higher doses of radioiodine administered. They concluded that prescribing a refined, less stringent diet that avoids high-iodine-containing foods would offer equivalent outcomes with increased patient convenience. This is because other factors which affect the uptake of radioiodine by the residual and metastatic tissue are: a) mass of iodine concentrating cells. b) avidity of iodine concentrating cells depending on their response to TSH and the TSH concentration c) availability of radioiodine as a result of the blood flow to the tissue and d) the distribution of labelled and stable iodine in the blood.

Doses of radioiodine given for whole body survey

The amount of remnant thyroid tissue left behind following thyroidectomy at the hands of a skilled surgeon is usually very small. Also, the uptake of ^{131}I by thyroid cancers, especially metastatic lesion, is not very high. Therefore, with small diagnostic doses, the detection of remnant or metastatic tissue many a times becomes difficult, due to inadequate counts resulting from low uptake. Hence, there is a tendency to give large diagnostic doses up to 1100MBq (30 mCi), so as to detect more foci of disease or functioning tissue [11.11]. However, reports suggest that smaller doses of up to 5 mCi (185 MBq) is unlikely to miss

'treatable' foci of functioning normal or cancerous tissue [11.11]. In addition, a very important observation made at Radiation Medicine Centre, Mumbai in early 1980's [11.12] that large amounts of radioiodine doses given for diagnostic survey may deliver enough radiation dose to the thyroid impairing its function and uptake and thereby adversely affecting the future therapy. This phenomenon first described by Rawson, et al. [11.13] and has been termed as "stunning" of thyroid which was subsequently confirmed by other groups [11.14-11.17]. This observation is not without controversy. Many workers refute stunning effect [11.18-11.21]. Recently Dam, et al. [11.22] have demonstrated that ^{131}I therapeutic efficacy is not influenced by stunning after diagnostic 185MBq (5 mCi) whole-body scanning.

Debates regarding thyroid stunning — a phenomenon whereby a diagnostic dose of radioiodine decreases uptake of a subsequent therapeutic dose by remnant thyroid tissue or by functioning metastases — have been fuelled by inconsistent research findings. Quantitative studies evaluating radioiodine uptake and qualitative studies using visual observations both compare thyroid function on the diagnostic scan (DxSCAN) versus the post treatment whole-body scan (RxWBS). The variability of findings may be the result of a lack of consensus in clinical nuclear medicine regarding many parameters of radioiodine usage including the need to obtain a pre-treatment diagnostic scan, appropriate therapeutic dose, time between therapy dose administration and DxSCAN, and how successful ablation is measured. In the studies those that used ^{123}I rather than ^{131}I for DxSCAN, allowed less time to elapse between diagnostic and therapy dose, and more time between therapy dose and RxWBS (at least 1 week), did not observe stunning. However, groups that recognized stunning did not demonstrate any difference in outcomes (determined by successful first-time ablation). Whether stunning is a temporary phenomenon whereby stunned tissue eventually rejuvenates, or whether observed stunning actually constitutes 'partial ablation', is yet to be delineated.

In the analysis a considerable number of patients when given large diagnostic doses often show evidence of a 'stunned' thyroid with an inadequate or poor response to therapeutic doses. In view of this observation of the phenomenon of stunning, due care is required to use smaller diagnostic radioiodine doses to detect residual thyroid tissue which is present after a near-total or total thyroidectomy. Hence, a dose of 1 to 2 mCi (37-74 MBq) is recommended. A post-therapy scan is always performed so as to detect any metastatic foci which may have been missed with smaller diagnostic doses. In this way prevented the phenomenon of a 'stunned' thyroid and also not miss any metastases.

Enhancement of radioiodine retention

Lithium carbonate has been used to enhance ^{131}I retention by the thyroid and metastases. At pharmacological levels, lithium decreases the release of iodine from the thyroid and the tumours [11.23]. A dose of 400-800 mg daily for 7 days prior to radioiodine therapy significantly increases uptake in metastatic lesions as compared to the normal tissues. In practice a good rise in TSH is sufficient to ensure enough endogenous stimulation and addition of lithium or other drugs is not warranted.

Ancillary techniques for stimulating uptake

a) Exogenous TSH can be given by injections. Bovine TSH stimulates uptake of radioiodine in normal and functioning thyroid cancer. However, the drawbacks like allergic reactions, neutralising antibodies against bovine and human TSH leading to TSH resistance has reduced its usage. Due to this, elevated endogenous TSH levels are preferred. The availability of recombinant human TSH (rhTSH) is now advocated and several trials have indicated its use

in stimulating the residual thyroid radioiodine uptake while according the advantage of no thyroxine withdrawal and lesser inconvenience to the patient.

Recombinant rhTSH or Thyrogen is used according to the following protocol. Before the first injection, base line blood samples are collected for TSH and thyroglobulin estimation. The patient is administered freshly reconstituted 0.9 mg rhTSH by an intramuscular injection on day 1 and 2. On day 3, ^{131}I tracer is given and imaging is done on day 4 and 5. A second blood sample is taken on day 5. This represents the stimulated sample. Human rhTSH has been recommended for the following categories of patients: a) those patients who have adequate thyroid hormone levels in circulation which precludes sufficient elevation of TSH following withdrawal of thyroid hormones b) patients intolerant of hypothyroidism following withdrawal of hormonal therapy c) patients with pituitary or hypothalamic insufficiency [11.24, 11.25].

b) Both acute and chronic administration of diuretics along with low dietary iodine helps to lower serum inorganic iodide and increase uptake. However, no added advantage has been observed [11.26]. In practice this method for increasing uptakes is not used.

11.2.2. Follow-up diagnostic whole body scans after ablation of remnant thyroid with radioiodine

All the earlier mentioned parameters are taken into consideration. The dose of ^{131}I used is 3-5 mCi. (111-185 MBq). This amount of activity is administered in order to have detectable counts in the smaller foci of metastases.

Radioiodine therapy following surgery of primary thyroid cancer

Radioiodine therapy of well-differentiated thyroid cancer involves the administration of large quantities of the radionuclide needed to destroy the cancer. As a result, radiation induced sequelae may manifest and hence, radioiodine therapy should be given after careful consideration and when there is a reasonable hope that it will benefit the patient. ^{131}I therapy for thyroid cancer has frequently been divided into radioiodine ‘ablation’ and radioiodine ‘treatment’ [11.27]. The term ‘ablation’ indicates administration of radioiodine to destroy the normal remnant thyroid tissue which is left behind either inadvertently or deliberately by the surgeon in an attempt to prevent any damage to the parathyroid glands, recurrent laryngeal nerves and other structures in the neck during the surgery [11.28].

The term radioiodine ‘treatment’ is often used to indicate treatment given to residual thyroid cancer in the thyroid bed as well as the treatment of recurrent disease in the thyroid bed and functioning metastases.

While there is no controversy regarding the treatment of metastatic disease or recurrent thyroid cancer in the thyroid bed with radioiodine, the problem arises in the treatment of the residual thyroid tissue remaining in the thyroid bed post-surgery [11.29-11.30]. The difficult question is to identify the presence of microscopic cancer cells which may be present among the normal thyroid cells. Herein lies the constant debate which has not yet been resolved.

Advocates for radioiodine treatment consider the following conditions:

- Residual thyroid cancer is present or likely to be present in the remnant thyroid tissue after surgery. This is based on the incidence of multicentricity or multifocality of thyroid cancers which is generally quite high and there is always a possibility of a focus

of cancer being present in the remnant thyroid after surgery. If there is pathological evidence of extra-thyroidal extension or capsular penetration of primary cancer then it would be prudent to consider the remnant to have residual thyroid cancer.

- Inadequate surgery has been performed, and the surgeon informs that thyroid tissue has been deliberately left behind.
- The residual thyroid cancer or normal tissue concentrates radioiodine
- The treatment with radioiodine will deliver an effective radiation dose to the cancer or thyroid tissue without risk of major complications.
- In the presence of normal residual thyroid tissue, the detection of distant metastases is difficult and often missed. This is because the radioiodine uptake function of normal tissue is greater than the metastatic tissue and diagnostic radioiodine doses are mopped up by the normally functioning residual tissues.

Uncertainty often arises in the interpretation of post-operative thyroid scans done with diagnostic doses of ^{131}I , 4-6 weeks after thyroid surgery, especially when the uptake is in or near the thyroid bed. After total thyroidectomy it is presumed that the uptake visualised in the thyroid bed is due to residual thyroid tissue. In the midline, the uptake is due to residual pyramidal lobe and/or thyroid cells in the distal thyroglossal duct and that immediately above the upper poles is due to residual tissue of the extension of the upper pole. As long as there is no pathological evidence of extracapsular or extra-thyroidal extension of the thyroid cancer seen on histology, these areas of radioiodine uptake can be presumed to be normal tissue. However, if there is evidence of extracapsular or extra-thyroidal extension and there is uptake in that portion of the thyroid bed, then it can be presumed that this could have residual thyroid cancer and should be treated for the same. The presence of residual thyroid cancer is more obvious when there is an incomplete surgery for removal of the primary cancer in biopsy proven inoperable cancers and in recurrent invasive cancer in thyroid bed.

Ablation of residual normal thyroid

The ablation of residual normal thyroid tissue although a widely practiced procedure remains controversial [11.31, 11.32]. It is because no randomized control trial is yet published in this field and there are many difficulties to realize this goal also in near future [11.33]. The proponents for the use of ^{131}I have shown evidence to suggest that ^{131}I destroys residual tissue and microscopic thyroid cancer which is difficult to detect clinically. Secondly, its use greatly simplifies the follow-up evaluation for secondaries especially using serum thyroglobulin as a tumour marker. In the presence of large remnant thyroid tissue, secondaries may remain undetected for long periods of time.

Papillary carcinoma of the thyroid tends to be bilateral, microscopically multicentric, metastasises to regional lymph nodes and has a higher incidence of persistent or recurrent disease. Both papillary and follicular cancers have a tendency to be invasive and locally infiltrate and this leads to a high probability for recurrence. This feature of invasiveness is often missed on histology if not looked for carefully. All these features argue for ablation of residual thyroid tissue. In a retrospective analysis of 1599 patients with differentiated thyroid cancer, it was observed that ^{131}I therapy was the single most important prognostic indicator by Cox proportional hazards regression model for prolonging “disease free survival” [11.6]. ^{131}I improved the outcome of high risk and low risk patients in this study. The incidence of recurrence was reduced by 50% in the low risk given ^{131}I for ablation of residual tissue. Even the incidence of pulmonary metastases was reduced by more than 50% when subtotal thyroidectomy was supplemented by ^{131}I treatment. Another large study of 1578 patients

reported from 13 Canadian hospitals where ^{131}I or external irradiation was employed for ablation of residual thyroid tissue, local disease in those with residual microscopic papillary cancer was controlled in 82-90% of patients as compared to 26% of those on T_4 suppression alone [11.24]. Similarly survival at 20 years was 90% in patients treated with ^{131}I or external irradiation while it was 40% when only surgery was performed. Strong support for use of extensive initial surgery and post-operative ^{131}I in papillary carcinoma with a tumour size more than 1 cm, showed a decreased risk of recurrence and death.

Another supportive study showed that, patients given ^{131}I to ablate normal residual thyroid tissue in low, intermediate and high risk groups, the incidence of recurrences was lesser in treated group as compared to those with only post-operative thyroid hormone therapy [11.5] especially when the tumour size was more than 1.5 cm. Radioiodine ablation prolongs life expectancy of patients who were apparently disease free after surgical treatment for thyroid cancer [11.32]. It was estimated that even the modest increase in the life expectancy shown was comparable to the absolute gain obtained by accepted medical interventions like screening mammography and lowering cholesterol levels in the blood.

In a 25 year prospective study, no patient died of cancer when complete ^{131}I tumour ablation was achieved, whereas 70% died with incomplete ablation. Nevertheless, there are reservations expressed by some physicians who have shown no benefit arising from treatment with ^{131}I of low risk group patients [11.35, 11.36]. Tumour recurrence, especially papillary cancer recurrence in regional lymph nodes is not associated with a fatal outcome. However, one should take local recurrence as a warning for adverse outcome which may precede or accompany distant metastases. A report in an International symposium in which 160 surgeons, endocrinologists, pathologists and nuclear medicine physicians participated, suggested a total thyroidectomy with post-operative thyroid remnant ablation, for most differentiated thyroid cancer regardless of patients age. Hemithyroidectomy was recommended for papillary cancer confined to one lobe or with ipsilateral nodes and follicular cancer confined to one lobe with minimal tumour capsular invasion. In another study of internationally recognized experts, total thyroidectomy was advised by 60% for papillary and 74% for follicular. Radioiodine for thyroid remnant ablation was recommended by 81% of respondents for papillary carcinoma and by 97% for follicular cancer [11.30]. In a recent meta-analysis of published literature on remnant ablation, Sawka, et al. [11.37] concluded that those who underwent remnant ablation, the evidence did support the reduction of relative risk of local and distant metastases.

Methods of ablation of residual/remnant thyroid tissue

The ablation of residual thyroid tissue can be achieved in three ways viz. with Low dose of ^{131}I , High dose of ^{131}I and calculated dose of ^{131}I .

High dose ablation

The first approach is the administration of high radioiodine doses varying from 2980-5550 MBq (80-150 mCi) ^{131}I as an inpatient therapy. The proponents of high dose ablation suggest that higher doses may actually be considered as a ^{131}I adjuvant radiotherapy for occult metastases not detected on diagnostic ^{131}I imaging studies [11.38-11.40]. The studies show that, 87% of patients with residual thyroid bed tissue can achieve total ablation with 3700-7400 MBq (100-200 mCi) and no significant increase was observed by giving higher doses. It was also suggested that, with low dose therapy where ablation rate is not as high, multiple small doses require multiple periods of hypothyroidism which is an inefficient, costly

approach that requires significant time investment on the patients' part. In fact, evidence suggests that sublethal radiation doses to the thyroid cells may decrease the biological half-life of subsequent radioiodine doses, thereby decreasing the effectiveness of therapy. The doses of radioiodine needed for ablation of normal thyroid tissue with high radioiodine uptakes are generally higher and these are more difficult to ablate.

The usual practice in treating thyroid cancer is to give a standard amount of ^{131}I to all patients. Most centres give between 100-200 mCi (3.7-7.4 GBq) and the doses of up to 7.4 GBq (200 mCi) are generally without serious complications [11.41]. A common variation is to adjust the amount of radioiodine based on the location of the cancer; 3.7 GBq (100 mCi) is given for presumed residual tissue in the thyroid bed, 5550-6475 MBq (150-175 mCi) give for lymph node metastases, 6475-7400 MBq (175-200 mCi) for lung metastases and 7.4 GBq (200 mCi) for bone metastases.

Low dose ablation therapy

McCowan, et al. [11.42] in 1976, reported that doses of 2960-3700 MBq (80-100 mCi) were not more effective than 1100 MBq (30 mCi). Subsequently, other retrospective studies, confirmed similar finding [11.42]. In addition, prospective studies reported by Creutzig [11.44], Johansen, et al. [11.45], Leung, et al. [11.46] and Bal, et al. [11.47] have also shown that ablation with low dose ^{131}I is as effective as high dose in achieving successful ablation with a single dose. An overall analysis of Radiation Medicine Centre experience in treating 579 residual thyroid tissue (Table 11.1) with radioiodine therapy 95.5% (553/579) of patient's residual thyroid can be easily ablated within two therapy sessions and only rarely does one come across patients who show radioresistance and require several dose schedules.

TABLE 11.1. RESPONSE OF RESIDUAL THYROID TISSUE TO ^{131}I THERAPY

Ablation	No. of therapies				
	1	2	3	4	5
Complete (n= 564)	499 (88.5%)	54 (9.6%)	5 (0.9%)	4 (0.7%)	2 (0.3%)
Partial (n= 6)	---	5 (83.3%)	---	1 (16.7%)	---
None (n= 9)	5 (55.6%)	1 (11.1%)	1 (11.1%)	2 (22.2%)	---

The philosophy of large dose ^{131}I ablation for remnant thyroid tissue is based on a contentious issue of "large dose not only ablates remnant thyroid but also ablates possible micrometastatic deposits". The proponents of initial high dose ^{131}I ablation argue that low doses are less effective for ablation of the micrometastases that are not visualized in post-therapy whole body scan, which at later date may result in higher local as well as distal recurrence rate. In a recent study, Mazzaferri and Jhiang [11.5] have reported no difference in long term tumour recurrence rate (7% versus 9%) between low dose 1073-1850 MBq (29-50 mCi) and high dose 1887-7400 MBq (51-200 mCi) ^{131}I remnant ablation groups.

Calculated dose ablation

The third approach is that of ablation based on radiation dose delivered rather than empirical administration of a fixed amount or varying amounts of radioiodine. This approach advocates individualized treatment so that each patient receives a maximum 'safe' dose of less than

200 rads to the blood and 4440 MBq (120 mCi) of ^{131}I retained at 48 hours after treatment. Average doses of 11433 MBq (309 mCi) 2775-24383 MBq (75-659 mCi) have been administered without permanent bone marrow suppression, leukaemia or pulmonary fibrosis [11.48]. The dosimetric calculations require determination of whole blood radioiodine concentration and whole body retention for 4 days after administration of tracer doses. Whole body retention may be calculated from urinary excretion or by counting the patient at a suitable distance from an uncollimated scintillation crystal. The results indicate that 3700-7400 MBq (100-200 mCi) usually eradicates uptake in iodine concentrating tissue in the thyroid bed or cervical lymph nodes. On the basis of radiation dosimetry it was estimated that a minimal dose required to ablate a normal thyroid gland is between 30-40 000 cGy and may be as high as 50 000 cGy and requires about 37 MBq (1 mCi) of ^{131}I per estimated gram of thyroid tissue [11.49]. In this study a detailed analysis was done on the use of low dose, high dose radioiodine and the radiation dose delivered to the residual thyroid tissue in the thyroid bed [11.50].

11.3. Optimisation of radiation dose and dose rate for ablation of remnant thyroid tissue

All patients were prepared for diagnostic ^{131}I studies by withholding thyroxine, all iodine containing medications and iodized salt for a minimum period of 4-6 weeks.

11.3.1. Diagnostic ^{131}I studies

Diagnostic ^{131}I studies were performed after an oral administration of 37-74 MBq (1-2 mCi) of ^{131}I . After 24 or 72 h, a neck scan was performed on a rectilinear scanner with 5" × 3" NaI (T1) crystal. A 1:1 dot scan was obtained with factors optimized depending on the count rate. Based on the visual analysis of these scans, thyroid remnants were considered to be present when discrete ^{131}I uptake was noted in the thyroid bed on the first postoperative study radioactive iodine uptake (RAIU) was measured by a conventional thyroid uptake probe and a standard iodine activity.

Mass of remnant thyroid was measured from the rectilinear scans. It was difficult to evaluate the depth of mass using information obtained from the surgeons regarding the thickness of tissue left behind during surgery, as it was empirical and differed from surgeon to surgeon. Also, the remnant tissue had been stimulated for 4 weeks by the rising TSH levels making this estimate fallacious. Therefore, it was felt that some other method was needed. Several patients who had received therapeutic doses of radioiodine were evaluated using a gamma camera, 72 h after background activity had reduced considerably. The aim was to obtain an idea about the depth of the residual tissue, as this was critical in measuring the volume. It was observed during these studies that the depth measured (as number of pixels) and was usually two-thirds of the breadth. Since most of the rectilinear scans showed residual tissue in the shape of an ellipse, the calculation of the volume was done using the formula:

$$\text{Volume} = \frac{4}{3} \times \frac{a}{2} \times \frac{b}{2} \times \frac{c}{2}$$

where a= length, b= breadth and c= depth of the tissue.

Rectilinear 1:1 dot scans were used to measure these parameters. The scatter correction factors were obtained by scanning several sizes of rectangular phantoms in a scattering medium (water) that contained concentrations of radioiodine varying from 0.15-11.1 MBq (4-300 μCi), which would correspond approximately to the amount of radioiodine trapped by the

residual tissue). Correction factors for scatter were estimated and applied to the measurement of the dimensions of the residual tissue visualized on the dot scan obtained on a rectilinear scanner.

11.3.2. Therapeutic ^{131}I studies

For calculation of radiation absorbed dose, it is essential to determine the parameters of RAIU (radioactive iodine uptake) in the target tissue, mass of the target tissue and the effective half-life of ^{131}I in the target tissue, after giving therapeutic doses of radioiodine. Since large radiation was being estimated, simple devices like a beta-gamma exposure rate meter (BGERM) had to be used for purposes of radiation protection.

The validity of using a portable BGERM for measuring ^{131}I in residual thyroid was established in four different ways:

- Using a portable BGERM and neck phantoms containing varying quantities of ^{131}I , it was noted that surface exposure rate of 500 $\mu\text{Gy/h}$ (50 mR/h) was equivalent to 37 MBq (1 mCi) of ^{131}I .
- An excellent correlation was observed ($r = 0.98$, $n = 18$, $p < 0.001$) when the RAIU in the neck obtained by BGERM method was compared with that obtained by the conventional probe method from a diagnostic ^{131}I dosage.
- The RAIU in the neck obtained after therapeutic ^{131}I was compared with the RAIU in the neck from a diagnostic dose in the same patient. A good correlation was obtained between therapeutic and diagnostic RAIU value ($r = 0.85$, $n = 30$, $p < 0.001$).
- The calibration of the ionization chamber was linear in doses ranging from 37 to 925 MBq (1-25 mCi).

From the sequential measurements of exposure rate for 3 or more days over the neck using BGERM, the biological half-life of the therapeutic dose of radioiodine was determined after applying corrections for physical decay. The effective half-life (T_e) was then computed using the biological half-life.

This is one of the few studies where actual quantitation of RAIU and T_e have been carried out after administration of therapeutic quantities of ^{131}I and not extrapolated from information obtained with diagnostic studies.

11.4. Criteria for therapeutic administration of radioiodine

Radioiodine was given for ablation of remnant thyroid when uptake of ^{131}I was greater than 0.1% and when discrete concentration was seen on the rectilinear scan images in the region of thyroid bed.

11.4.1. Ablation criteria

Diagnostic studies were repeated with 3-5 mCi (111-185 MBq) of ^{131}I , 4 to 6 months after therapy. A rectilinear 1:1 dot scan of the neck was obtained routinely. RAIU was measured by a conventional thyroid uptake probe. A chest X ray and serum thyroglobulin were also routinely advised. Ablation of the thyroid remnant was considered when RAIU was less than 0.1%, no visual evidence of radioiodine concentration on the 1:1 dot scan and a serum thyroglobulin concentration of less than 10 ng/ml. The criterion for partial ablation was the

visualisation of discrete concentration of ^{131}I in the thyroid bed even though the uptake was less than 0.1%.

11.4.2. Initial dose rate calculation

The general expression for the dose rate in a tissue containing a concentration of 'C' MBq per gram of tissue emitting 'j' types of radiation with effective energies for the radiation of type j, respectively is:

$$D = 0.58C \sum E_j \phi_j \text{ Gy/hr}$$

where E_j is the mean energy (in MeV) for radiation j and ϕ_j is the absorbed fraction in that specific tissue of the radiation type j.

It is assumed that the tissue dimension of the remnant is 5-50 mm, in which case all non-penetrating radiations, such as beta particles and conversion electrons, are completely absorbed in the target tissue ($\phi_j = 1$) and the penetrating radiations e.g. 364 and 637 KeV photons contribute only a small fraction of the total absorbed dose (i.e. $\phi_j = 0$). Using ICRP data for analysis the dose rate to tissue containing 'C' MBq/g of ^{131}I is given by:

$$D = 0.58 \times 0.19C = 0.11 C \text{ Gy/hr}$$

11.4.3. Cumulative absorbed dose

Assuming a monoexponential washout of ^{131}I from the tissue, the T_e is calculated. Dose D to the tissue is calculated from the initial dose rate D_0 (using the previous equation) as follows:

$$D = 1.44 T_e D_0 \text{ Gy}$$

where $D_0 = 0.11 C_0 \text{ Gy/hr.}$, where C_0 (MBq/g) is the initial (24 hr) concentration of ^{131}I in the tissue and is related to the total activity Q (MBq) administered to the patient as follows:

$$C_0 = Qf/100 \text{ MBq/g}$$

where 'f' is the percentage uptake per gram in the tissue at 24 hours.

Histological classification of the thyroid cancers in this study showed papillary and mixed (papillary and follicular) cancers in 60% and follicular cancers in 40% of the patients. The mean age of the patients was 35 ± 9.4 years and male to female incidence was 1:2. The main advantage of individualized ablation is that no patient receives more whole body radiation than is necessary. And, also no patient receives an amount of radioiodine which is certain to be inadequate to achieve complete ablation.

11.5. Calculated dose ablation

A prospective analysis on 95 patients was undertaken. Before therapy, the amount of therapeutic activity required to deliver 30 000 cGy to the remnant thyroid tissue was calculated from the knowledge of various physical and biological dosimetric parameters obtained from 100 μCi ^{131}I diagnostic studies.

Figs 11.1, 11.2, 11.3 and 11.4 show that 81.9% (77/94) of patients were given a therapeutic activity of 1750 MBq (50 mCi) or less. Of these, 80.5% (62/77) of patients achieved complete

ablation of residual thyroid tissue, substantiating the fact that calculation of dose has been useful in keeping the administered doses within 1750 MBq (50 mCi).

A cumulative dose of 30 000 cGy and an initial dose rate of 500 cGy/h or more should be delivered in order to achieve ablation in almost 90% cases. This conforms to earlier retrospective study, again emphasizing the need to calculate and tailor radioiodine doses as per the patients' need. Remnant thyroid with mass less than 2 gms can be more easily ablated. Hence both the retrospective and prospective studies indicate that calculation of doses for individual patients is reliable and necessary. However, if facilities do not exist at some centres then fixed dose of 1750 MBq (50 mCi) can be administered expecting ablation in almost 85-86% of patients. 1750 MBq (50 mCi) is needed in about 84% of patients to be effective in producing ablation and this conforms to the proponents of low dose radioiodine therapy. Some authors, however, feel that 1100 MBq (30 mCi) as an outdoor treatment will still be inadequate and the doses need to be increased to 1480-1550MBq 40-50 mCi. In a recent prospective randomized trial Bal, et al. [11.51] have also demonstrated in 509 patients that any dose of ¹³¹I between 925-1850 MBq (25-50 mCi) is adequate enough to ablate remnant thyroid tissue with a acceptable 20% failure rate [11.51].

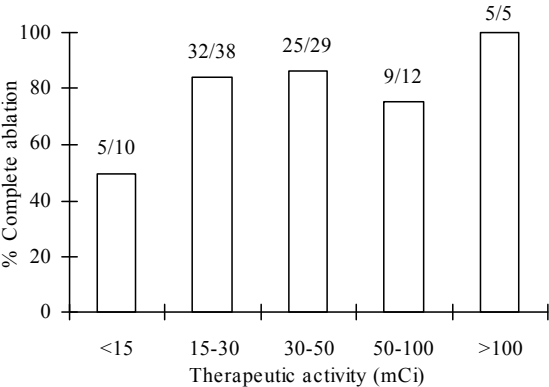


FIG. 11.1. A bar diagram showing the ablation response of remnant thyroid tissue following calculated therapeutic dosages.

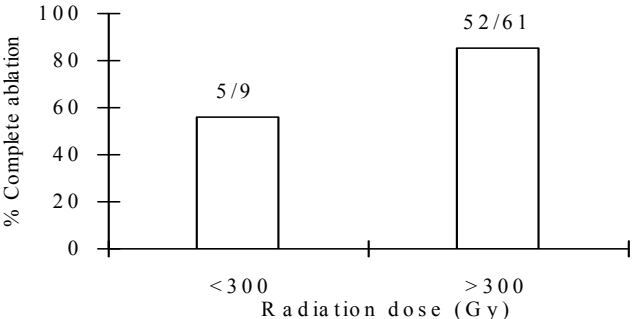


FIG. 11.2. A comparison of ablation response of remnant thyroid tissue at a radiation dose of 300 Gy and less and more than 300 Gy.

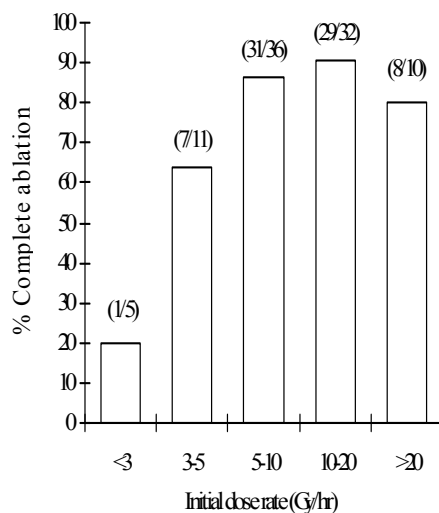


FIG. 11.3. A bar diagram illustrating the treatment response at initial dose rate of 5 Gy/h and less and more than 5 Gy/h.

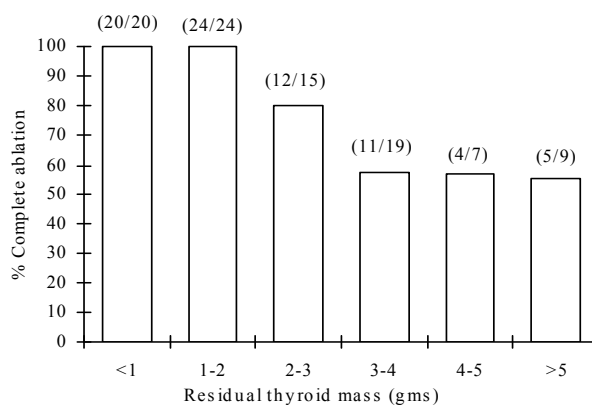


FIG. 11.4. A bar diagram showing the effect of mass of remnant thyroid tissue on the treatment response.

Another significant study from India [11.47] in 149 randomly selected patients with only remnant thyroid tissue, administered activities were (a) 925-1258MBq [25-34 mCi (30 ± 1.5)] in 27 patients, (b) 1295-2368 MBq [35-64 mCi (50.6 ± 5.4)] in 54 patients, (c) 2405-4403MBq [65-119 mCi (88.6 ± 14)] in 38 patients and (d) 4440-7400 MBq [120-200 mCi (155 ± 28.7)] of ^{131}I in 30 patients, (Table 11.2). Six month to 1 year after treatment, all subjects were reassessed after withdrawing L-thyroxine medication for 4-6 weeks. A step-wise logistic regression analysis using ablation (successful or not) as a dependent variable and age, sex, type of surgery, histopathology and individual ^{131}I administered activity as explanatory or predictor variable was performed using BMDP package.

It was observed a complete ablation of 63% (17/27) in patients treated with 1100 MBq (30 mCi), 77.8% (42/54) in patients treated with 1750 MBq (50 mCi), 73.7% (28/38) in patients treated with 3330 MBq (90 mCi) and 76.7% (23/30) in patients treated with 5735 (155 mCi), (Table 11.2 and 11.3). The dosimetry calculations showed that the dose delivered by administration of 1110, 1850, 3330, 5735 MBq (30, 50, 90 and 155 mCi) of ^{131}I was

approximately 20 000 cGy, 30 000 cGy, 50 000 cGy and 130 000 cGy, respectively. The adequacy of surgery was an important independent prognostic factor in multivariate analysis ($p < 0.05$), which influenced the remnant thyroid ablation. Surprisingly ^{131}I administered activity had no effect on the same ($p > 0.3$).

TABLE 11.2. DEMOGRAPHIC PROFILE OF FOUR RANDOMIZED GROUPS OF PATIENTS TREATED WITH DIFFERENT DOSES OF RADIOIODINE ^{131}I
(data on patients of All India Institute of Medical Sciences, New Delhi)

Patient characteristics	Radioiodine dose			
	925- 1295MBq (25-35 mCi)	1295- 2368MBq (35-64 mCi)	2405- 4403MBq (65-119 mCi)	4440- 7400MBq 120-200 mCi
Total number of patients	27	54	38	30
Age mean years (range)	38 (25-59)	37 (24-58)	40 (25-62)	39 (27-68)
Sex (Female : Male)	20:7	42:12	23:15	19:11
Histology (Pap ^a : Foll ^b)	22:5	28:26	18:20	19:11
Type of surgery (NTT ^c : Subtotal)	26:1	45:9	30:8	21:9
Pre-ablation RAIU ^d at 48 hrs (mean)	6.6%	6.2%	5.6%	8.4%
Range	2-15.6%	1.6-19.8%	3.5-12.4%	1.8-17.7%

^a Papillary carcinoma.

^b Follicular carcinoma.

^c Near total thyroidectomy.

^d Radioactive iodine uptake.

TABLE 11.3. SUCCESSFUL ABLATION WITH VARIOUS DOSES OF RADIOIODINE THERAPY

Administered dose MBq (mCi)	925-1295MBq (25-35 mCi)	1295-2368MBq 35-64 mCi	2405-4403MBq 65-119 mCi	4440-7400MBq 120-200 mCi
Mean activity MBq (mCi)	1110± 55.5 (30 ± 1.5)	1872.3±199.8 (50.6 ± 5.4)	3278.2± 518 (88.6 ± 14)	5735± 1061.9 (155 ± 28.7)
Absorbed dose (cGy)	19,800 ± 992	31,372 ± 3355	49,616 ± 7858	130,200 ± 24,162
Successful ablation (%)	17/27 (63)	42/54 (77.8)	28/38 (73.7)	23/30 (76.7)

Values are expressed as mean ± SD. Statistical analysis of patient characteristics such as age, sex, percentage uptake, type of surgery and histology between those who had ablated and those failed, revealed no significant difference (chi square test).

11.6. Radioiodine treatment for thyroid cancer

This terminology has been adopted to differentiate radioiodine ‘ablation’ of normal remnant thyroid tissue from patients with proven or recurrent thyroid cancer or treatment of functioning metastases.

The following categories of patients are included this group:

- Inoperable primary;
- Postoperative residual disease in the neck as indicated by surgeon;
- Invasion of thyroid capsule and extra-thyroidal spread indicated at surgery and on histopathology;
- Recurrent thyroid cancer;
- Loco-regional spread to neck nodes;
- Distant metastases.

There is hardly any controversy regarding radioiodine treatment of this category of patients. However, as is true for ablative dose determination there are differing theories on the activity of ^{131}I needed for proper therapy.

11.6.1. Treatment of cervical nodal metastases

In the treatment of cervical nodal metastases, predominantly two approaches are followed. One approach is to give a standard fixed dose of activity and the other involves a calculated activity approach. A fixed dose method is easier to follow and hence recommended by many centres. The protocol used is 150 mCi (55.5 GBq) for treatment of cervical node metastases. The maximum suggested doses were 7400 MBq (200 mCi), as an early study by the IAEA subcommittee on human use had found that doses higher than 7400 (200 mCi) were not more effective for ablation of nodes rather produces unnecessary whole body radiation dose to the patient. This fixed dose regime has been reported to be effective, safe and time and cost efficient. When enlarged nodes are confirmed to be malignant by fine-needle aspiration biopsy, the therapy of choice is usually surgical resection. However, increasingly sensitive power Doppler sonography can lead to the discovery of small masses or nodes that may be amenable to radioiodine therapy. Large lymph node metastases (>1 cm in diameter) are usually only partially responsive to ^{131}I treatment, and surgery can be undertaken as a first-line treatment. At Memorial Sloan–Kettering, Robbins, et al. found that a single dose of radioiodine can abolish subsequent locoregional uptake of radioiodine in approximately 65% of patients [11.52]. Selected centres use dosimetry in such patients to administer the maximal safe dose; however, most centres will administer an empiric activity, such as 3.7 or 5.5 GBq (100 or 150 mCi).

In practice the above regimen was followed. Patients with cervical nodal metastases with an adequate neck uptake are given 150-180 mCi. (55.5-66.6 GBq) Table 11.4.

TABLE 11.4. RESPONSE OF NODAL METASTASES TO ^{131}I THERAPY

Ablation response	No. of therapies				
	1	2	3	4	≥ 5
Complete (n = 378)	287 (75.9%)	67 (17.7%)	15 (4.0%)	5 (1.3%)	4 (1.1%)
Partial (n = 20)	9 (45.0%)	6 (30.0%)	2 (10.0%)	2 (10.0%)	1 (5.0%)
None (n = 44)	32 (72.7%)	7 (15.9%)	-	4 (9.1%)	1 (2.3%)

11.6.2. Quantitative dosimetry therapy

The quantitative dosimetric approach is termed BEL dosimetry. A dose can be selected which will deliver 200 cGy to the blood with no more than 4440 MBq (120 mCi) retained in the body at 24 hours and 2960 MBq (80 mCi) or less at 48 hours in the presence of lung metastases. Using this approach, doses calculated between 3108-20017 MBq (84-541 mCi) have been given to 44 patients. Others have restricted the highest to 11100 MBq (300 mCi) using the same approach [11.53]. Very high doses pose problems of radiation side effects for patients and also very strict and stringent radiation safety measures are needed to be followed.

The interest in the above protocol lies in the fact that the effective half-life and uptake of ¹³¹I varies from patient to patient and hence a calculated dose is more effective than a fixed standard dose. Another dosimetric approach propagated by University of Cincinnati group [11.49] is based on the delivery of 8500 cGy for the treatment of nodal metastases. These doses are based on calculations done from tracer studies utilising data of mass of nodal metastases, uptake and effective half-life. This modality of calculation of dose had shown a successful ablation of lymph node metastases in 74% of patients with a single dose therapy.

In this series, response to radioiodine treatment was studied in 448 patients having cervical nodal metastases. Of the 448 patients, 382 (85.3%) patients showed complete ablation and 21 (4.7%) showed partial ablation of nodal metastases. Out of the 382 patients, complete ablation was achieved in 290 (75.9%) patients with a single therapy, remaining patient needed more doses. In spite of several therapies, 5 (11.1%) patients showed no response. The radioiodine dose required for complete ablation ranged from 5.55-25.9 GBq (150-700 mCi) with a mean dose of 14.8 GBq (400 mCi).

11.6.3. Radioiodine treatment of distant metastases

Radioiodine therapy has been used to control distant metastases from differentiated thyroid carcinoma for more than 50 years [11.1]. It was clear early on that metastatic lesions only had a small fraction of the iodine avidity that normal thyroid tissue exhibited. The most common distant metastatic sites are lungs, spine, and appendicular bone. The standard preparation for radioiodine therapy of distant metastases involves withdrawal of thyroid hormone to elevate the TSH level. There is no evidence that higher TSH levels provide any better outcomes than those just above 25-30 mU/L. Occasionally, widespread differentiated thyroid carcinoma can produce thyroid hormone, which prevents a significant elevation of TSH. The activity administered may be empiric, ranging from 3.7 to 11.1 GBq (100-300 mCi), or may be tailored according to dosimetric studies. At the present time there is no evidence that one approach results in a better outcome than the other.

Radioiodine therapy of pulmonary metastases

The treatment of pulmonary metastasis of differentiated thyroid cancer is primarily based on radioiodine therapy. The reasons for this are two fold. Firstly, pulmonary metastasis tend to be bilateral, multimacronodular or micronodular and secondly, they may not concentrate radioiodine. Hence radioiodine is the treatment of choice for pulmonary metastasis concentrating radioiodine while in noniodine concentrating metastasis the treatment is limited to a wait and watch policy or at the most chemotherapy (which usually is ineffective) can be given. The attempts to calculate radioiodine dose for effective therapy are negligible, if absent. This is primarily because of the difficulty of estimating mass, iodine uptake in metastasis, the biological half-life, and other parameters required for dose calculations. So

treatment is generally empirical. The tendency is to give smaller doses because of the fear of inducing radiation fibrosis as a long term sequelae.

Measurement of pulmonary radiation dose and biological half-life

To calculate the radiation dose delivered to the lungs from the administered therapeutic dose, it was necessary to measure the biological half-life of deposited radioiodine in the lungs using a portable BGERM [11.50]. Patients were treated with single dose not exceeding 10 GBq (270 mCi). For radiation safety reasons, the patients were hospitalized in an isolation room. To determine whether an appreciable amount of ^{131}I had concentrated in lung tissue, exposure rates were measured by placing the BGERM on the posterior chest region over the left and right sides. A reading greater than the exposure rate over the thigh region (body background) indicated the presence of ^{131}I in lung tissue. Serial readings were obtained daily for 4-6 days after ^{131}I therapy. A minimum of three consecutive measurements were obtained to calculate radioiodine biological half-times in the lungs. The assumption was that there was homogeneous distribution of radioiodine in lung tissue.

With the above relationship, radioiodine uptake in lung metastases was calculated as a percentage of the administered dose after converting the BGERM exposure rate measurement to GBq of radioiodine present in the lungs. From sequential exposure rate readings, the biological half-life of ^{131}I in lung tissue was calculated. An absorbed dose was calculated using these parameters and assuming a lung mass of 810 g. Lung mass was obtained during evaluation of dimensions of a Indian standard man by the Health Physics Division of Bhabha Atomic Research Centre. The cumulative absorbed dose to lung tissue was estimated using MIRD methodology.

The approach to the treatment of pulmonary metastases with radioiodine is empirical primarily because the calculations of effective half-life, lung uptake and mass calculations are difficult and many assumptions are to be made before such techniques are feasible. There were 101 patients of lung metastases who had received radioiodine therapy. Complete ablation of lung metastases was possible in 46.5% (47/101) cases only. In this group about 83% (39/47) of the patients showed complete clearance of lung metastases with three therapies. No response was observed in 20.8% (21/101) of cases. Of these 21 cases 23.8% (5/21) showed no response even after four or more therapies. The remaining patients were fresh cases under evaluation.

Patients with lung metastases show extremely variable clinical behaviour, ranging from fatal outcome to complete disease remission. Factors which affect the prognosis are not clear. Previous observations suggest that micronodular lung metastases are associated with a favourable prognosis [11.54, 11.55]. On one hand no significant results using radioiodine therapy in lung metastasis have been reported [11.56]. On the other radioiodine therapy in cumulative doses of 5.55 GBq to 29.6 GBq along with LT_4 suppressive therapy were shown to produce good ablation of lung metastases. The follow up period was from 2-25 years.

Radioiodine therapy of skeletal metastases

Many anecdotal reports and several series on the use of radioactive iodine therapy for bone metastases are in agreement that bone metastases are generally resistant to commonly used activities of ^{131}I , which may be related primarily to the usual large mass of bone metastases at their discovery [11.57-11.60]. A retrospective report from the Mayo Clinic described 85 patients with metastatic differentiated thyroid carcinoma [11.61]. At 10 y, 75% of the patients

had died. Univariate analysis found that radioiodine uptake by lesions was associated with a better prognosis; however, this did not hold up under multivariate analysis, which found that older age and multiple organ sites were the only significant predictors of cancer mortality.

Dosimetry of bone metastases has not been reported so far. However, the bone lesions are generally large and multiple and hence adequate ablative radiation doses are very rarely achieved. There were 177 patients treated with RMC with radioiodine for bone metastases. Of these 3.4% (6/177) cases showed a complete regression of bone metastases and 37.3% (66/177) showed a partial response where in the uptakes were reduced in some metastatic sites and not in other lesions. No response to therapy was observed in 59.3% (105/177) of the patients. Though there was a very poor response for bone metastasis but a marked improvement in quality of life was noticed. There was significant reduction in bone pains & metastatic masses; and most rewarding was to see paraplegic patients walking after one to two therapies.

11.6.4. Outcome of radioiodine therapy for skeletal metastases

Mortality was very high, almost 75% in the first few months in those patients not treated with radioiodine. These were patients who generally presented at the first visit in a very poor state of health with extensive disease. In patients treated with ^{131}I , two important effects of radioiodine therapy were observed. The first was that despite the presence of bone metastases the five year survival was 50%. The second was that patients with bony metastases survive almost 15-18 years. The improved quality of life and extended survival in spite of extensive skeletal disease is a direct result of the benefits of radioiodine treatment. The benefits of radioiodine therapy for skeletal metastases are improved quality of life, moderately prolonged survival and delayed onset of recurrences.

11.6.5. Non-iodine concentrating metastasis and management

Bone metastases generally tend to become non-functional only when radioiodine therapy has been given. The reason as to why there is a loss of iodine trapping function during the course of the disease is not clear. One of the theories postulated is the change in character of the tissue from a differentiated to a dedifferentiated state occurring as a result of radioiodine therapy and radiation damage, the loss of iodine transport mechanisms of the tumour cells which might be more radiosensitive than other cell functions or persistence of radio resistant cell populations in the tumour with poor iodide trapping function. The mortality due to non-functioning metastases disease was high. Forty-three per cent (43/103) of patients in this group died within a span of five years. In contrast, 10.8% of the patients with functioning metastases disease died in five years. Hence, non-functioning metastatic disease carries a grave prognosis.

A survey of non-iodine concentrating metastases reported in the literature indicates that this is not an uncommon finding. About 50% of distant metastases fail to concentrate ^{131}I , even after adequate patient preparation and large diagnostic doses. Reports of a large Canadian series [11.34] indicated that 33% of follicular and 50% of papillary carcinomas tend to show no iodine trapping in distant metastases. The incidence in women was higher than in men.

In some instances, ^{131}I concentration was inhibited by contrast material given for CT scans or X ray procedures performed as a part of patient investigation prior to whole body ^{131}I diagnostic scans. Hence the importance of adequate information on patient investigations is a mandatory requirement. In some cases, the functioning tumour or large amounts of residual

thyroid synthesize and release enough thyroid hormones in circulation so that TSH levels are suppressed. There is inadequate stimulation of tissue and radioiodine therapy would be ineffective, as sufficient quantity of radioiodine for cytolysis cannot be achieved. The reduced diagnostic radioiodine uptakes will give a false impression of poorly functioning or non-functioning disease.

11.7. Radioiodine therapy for patients with negative diagnostic scans and elevated thyroglobulin levels

Elevated serum thyroglobulin (Tg) levels in patients with thyroid cancer after thyroidectomy and radioiodine ablation is a good indicator of presence of metastatic or recurrence of thyroid cancer tissue. The dilemma as to whether to treat such patients with therapeutic doses of ^{131}I is always being questioned. There has been a trend toward using radioiodine therapy for thyroid cancer survivors who have elevated serum Tg levels, even in the absence of identifiable lesions [11.62-11.64]. Several small series have reported that lesions can often be seen on scans after therapy and that subsequent serum Tg levels are often lower. Other investigators also find that this strategy occasionally helps localize occult disease. However, they recommend against widespread use of radioiodine therapy in all patients who have mild elevations of serum Tg in the absence of radiologically identifiable disease [11.65, 11.66]. It is likely that patients seen at different stages of follow-up have been mixed in these studies, and more recent studies have shed light on this issue. Two-thirds of patients who have detectable serum Tg after TSH stimulation and no other evidence of disease at one year after initial therapy will normalize their serum Tg at the subsequent control TSH stimulation, in the absence of any further treatment. This is the result of the disappearance of benign or malignant thyroid cells that have been irradiated and disappear slowly. In patients with persistent cancer, the serum Tg will gradually increase, and this trend will define a group needing additional treatment. However, in the absence of any alternative line of treatment it would be worthwhile to extend this experience to a larger group of patients.

11.8. Conclusion

Radioiodine has a major impact on the progressive control and cure of thyroid carcinoma. There is agreement that ^{131}I remnant ablation reduces local recurrence rates after total or near-total thyroidectomy, in those at higher risk for recurrence. It is very useful for iodine-avid disease that is not surgically accessible, especially diffuse lung metastases in younger individuals. Its efficacy in older individuals with large metastases is considerably lower but still poorly defined. More epidemiologic studies on the incidence and prevalence of complications of ^{131}I are needed to enable us to better define the risks and benefits of this therapy. The growing knowledge of how ^{131}I is incorporated into metastatic lesions, of the factors which can prolong its occupancy time, and of the development of lesion dosimetry methods will undoubtedly alter its usage pattern in the future. However, it has been acknowledged over the years that radioiodine is not a panacea. It has significant side effects that must be considered in determining the risk-to-benefit ratio for each patient.

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12. PRACTICAL ASPECTS OF RADIOIODINE THERAPY

12.1. Introduction

Radioiodine therapy, while being simple and effective, does involve the use of a relatively toxic radionuclide. There are both internal and external radiation hazards, and potential effects on the patient and their family, as well as for treating personnel, which must be considered. Stringent precautions must be taken by staff at all phases of the treatment to avoid accidents. This section will endeavour to canvas all these aspects, and to provide the necessary information for persons involved in the therapy. Some case studies are included to illustrate the hazards involved. These are based on real incidents.

12.2. Selection of a therapeutic radionuclide for thyroid cancer treatment

In case of thyroid disease, the selection of the element to use is obvious, given the high selectivity of the thyroid for iodine. What is not so obvious is just which isotope of iodine.

The main characteristics for therapeutic iodine radionuclide are:

- A physical half-life similar to the biological half-life (clearance);
- A high percentage of locally absorbed radiations — low energy electrons, Auger electrons and alpha particles have a very localized effect due to their poor penetration in tissue;
- Minimal high energy photons;
- Easy availability at a reasonable price;
- High specific activity and appropriate chemical form.

12.2.1. *Half-life*

The physical half-life of a radionuclide is the time taken for the radioactivity to decrease to 50% of its original level. The biological half-life is the half clearance time of that radionuclide or labelled compound from the body. If the biological half-life is much larger than the physical half-life, the time course of the radionuclide's effect is limited only by its physical half-life. Excretion of the radionuclide before it has substantially decayed is inefficient radiobiologically. Half-life is discussed in more detail later.

12.2.2. *Locally absorbed radiations*

The shorter the range of a radiation, the more of its energy is absorbed at the cellular or organ level and the lower the particle energy, the higher the absorption. Particles such as alpha, beta and Auger electrons are all strongly absorbed. Gamma rays (photons) on the other hand — unless very low energy — are far less absorbed, and can pass through tissue. High energy gamma rays have relatively low absorption.

12.2.3. *Specific activity and chemical form*

This is the amount of radioactivity per unit mass. The higher the specific activity, the more radio activity is available to the thyroid. The chemical form must be such that it is easily absorbed by the body, and preferably orally administered. There are a number of iodine isotopes, and of the radioactive forms, only ^{131}I meets the criteria outlined.

12.3. Physical characteristics of Iodine-131

^{131}I is a reactor-produced radionuclide, not occurring naturally. Its value in the diagnosis and treatment of thyroid disease was recognized in the early 1950s, and it has been in continuous use ever since.

Some relevant physical properties of ^{131}I are shown in Table 12.1 [12.1].

TABLE 12.1. PHYSICAL PROPERTIES OF ^{131}I

Main gamma emissions (and abundance)	284 keV (6%), 364 keV (82%), 637 keV (7%)
Main beta emissions (and abundance)	248 keV (2%), 334 keV (7%), 606 keV (90%)
Main electron emissions (and abundance)	46 keV (4%), 330 keV (2%)
Mean range of beta particles in thyroid	~ 0.5 mm
Physical half-life	8.04 days
External exposure from point source in air:	
skin dose (betas, electrons)	$7.7 \times 10^{-3} \text{ mSv.MBq}^{-1}.\text{hr}^{-1}$ at 100 cm
deep tissue dose (photons)	$6.6 \times 10^{-5} \text{ mSv.MBq}^{-1}.\text{hr}^{-1}$ at 100 cm
source in glass vial	$6.4 \times 10^{-5} \text{ mSv.MBq}^{-1}.\text{hr}^{-1}$ at 100 cm
Half value thickness in:	
lead	3 mm
steel	23 mm
Tenth value thickness in:	
lead	11 mm
steel	56 mm

From Table 12.1 shows that the half-life is nearly ideal, and there are many beta and electron emissions, at reasonably low energies. There is also considerable gamma ray emission, which is a safety disadvantage in protection of persons in the vicinity of the patient, but allows imaging of biodistribution. Iodine is also easily available as a pharmaceutical in high specific activity in the form of potassium or sodium iodide (either liquid or in capsule form), both of which are readily and efficiently absorbed in the gut. The biodistribution of iodine includes not only the thyroid, but also kidneys/bladder, salivary glands, and gut. Whilst low in uptake compared to the thyroid, they are still significant when the radiation dosimetry of ^{131}I is considered.

12.4. Radiation quantities and units

As units will be mentioned many times in this monograph, a short summary of the radiation quantities and their measurement units is presented here.

Exposure E

Exposure is the amount of ionisation created in air by ionising radiation, and has the unit of Coulomb per kilogram (C.kg^{-1}). It is only defined for air, and is the easiest measured quantity.

Absorbed dose D

When ionising radiation is absorbed in a target material, energy is transferred to the target. Absorbed dose is the amount of energy per unit mass, and can be used in any material, although it is not easily measured directly. It has the unit of Joules per kilogram ($\text{J}\cdot\text{kg}^{-1}$), or the special name Gray (Gy).

Absorbed dose can however be determined from a measurement of exposure in air if certain characteristics of the target material are known. For photons in air for example, the relationship is:

$$\text{Absorbed dose} = \text{exposure} \times 0.877$$

In radiation safety practice, it is often assumed that the factor is approximately 1, thus simplifying measurements. Many radiation measuring instruments have a built in factor for tissue, and read directly in Gray, even though it may be exposure which is being measured. As Gray is a large dose, usually submultiples such as microGray (μGy) and milliGray (mGy) are used.

Equivalent dose H

Different types of radiation have varying biological effects in human tissue, for a given amount of absorbed dose. This is taken into account by use of the *Radiation Weighting Factor* W_R , which ranges from a value of 1 for gamma rays and X rays, and electrons of all energies (including beta particles), to 20 for a range of neutron energies, and for alpha particles. The equivalent dose is determined by adding together the product of absorbed dose and W_R for each contributing radiation.

In the case of ^{131}I however, the concerns are with photons and electrons, hence:

$$\text{Equivalent dose } H = \text{Absorbed dose } D$$

The unit of equivalent dose is the Sievert (Sv). Again submultiples are used.

Effective dose E

Not all human tissues have the same sensitivity to radiation. For example breast tissue is far more sensitive than skin. So the potential biological effect of a radiation exposure which involves more than one tissue type, this must be taken into account. Current ICRP recommendations [12.2, 12.3] describe a range of *Tissue Weighting Factors* W_T (see Table 12.2). The effective dose is then calculated as the sum of $H \times W_T$ for all exposed tissues. The unit of effective dose is also the Sievert (Sv).

Activity

The amount of activity of a substance is measured in Becquerels (Bq). 1 Bq is one nuclear decay per second. One Becquerel is a very small quantity, so multiples such as Mega-Becquerel MBq (1 000 000 Bq) and Giga-Becquerel GBq (1000 million Bq) are used. The specific activity is the radioactivity per unit mass or volume. It could also be thought of as concentration.

TABLE 12.2. TISSUE WEIGHTING FACTORS

Tissue or organ	Tissue Weighting Factor WT	Sum of tissue Weighting Factor WT
Gonads	0.08	0.72
Bone marrow (red), Colon, Lung, Stomach Breast, remainder tissues*	0.12	0.08
Bladder, Oesophagus, Liver, Thyroid	0.04	0.16
Bone surface, Brain, Salivary glands, Skin	0.01	0.04

*Remainder Tissue: Adrenals, extrathoracic (ET) region, gall bladder, heart, kidneys, lymphatic nodes, muscles, oral mucosa, pancreas, prostate, small intestine, spleen, thymus, uterus/cervix.

Conversion factors for units

The above units are all metric or SI (Système Internationale) units, as used in the IAEA Basic Safety Standard (BSS) [12.4]. In many parts of the world however, the older units are still in use. Table 12.3 shows both units, and their conversion factors. The unit in use must be clearly understood, as many accidents have occurred when someone assumed same unit when in fact it was the other. In the case of radioactivity, this can mean a huge error.

TABLE 12.3. CONVERSION FACTORS

SI Unit	Non-SI Unit	Conversion
Coulomb per kilogram (C.kg ⁻¹)	Roentgen (R)	1 C.kg ⁻¹ = 3876 R
Gray (Gy)	Rad	1 Gy = 100 rad
Sievert (Sv)	Rem	1 Sv = 100 rem
Bequerel (Bq)	Curie (Ci)	1 Bq = 2.7 × 10 ⁻¹¹ Ci

Half-life — physical, biological and effective

The physical half-life T_p of a radionuclide is simply the time required for the activity to reduce to 50% of an initial level, and in the case of ¹³¹I, it is 8.04 days.

Similarly, the biological half-life T_b is the time taken for 50% of an substance (whether radioactive or not) within the human body to be excreted by whatever means. There are two phases of excretion — unbound (that fraction not extracted by thyroid tissue from the blood) and bound (that fraction taken up by thyroid and other tissues) radioiodine. In the case of unbound radioiodine, the biological half-life is only a matter of hours. For bound radioiodine, the biological half-life will vary from patient to patient, depending on the amount of thyroid tissue, their thyroidal hormonal status, and the presence of any metastatic deposits, and is very much longer compared to the physical half-life. Radiation safety considerations are based on the bound fraction during the hospital stay, and the unbound fraction following discharge.

The effective half-life T_e is a combination of the physical and biological half-lives, according to the formula:

$$1/T_e = 1/T_p + 1/T_b$$

Calculation of the effective half-life is not required due to simple assumptions. In the initial phase, the effective half-life can easily be measured from the reduction in radiation emitted by the patient over the first few days following administration, and is around 24 hours. In the second phase, the biological half-life is so long compared to the physical half-life (about 80 days [12.5]) that the effective half-life can be simply taken to be equal to the physical half-life.

12.5. Risks associated with radioiodine therapy

There are three source of potential radiation exposure from radioiodine therapy — external (photon) radiation emitted by the patient and any other source, internal contamination from ingestion or absorption of spilt radioiodine-containing waste, and inhaled airborne contamination from volatilized iodine. Of these, the external radiation hazard is the least critical, although still highly relevant. As the thyroid radiation dose from ^{131}I is about 3.2 mGy/MBq using 25% uptake [12.6], even a small ingested activity is significant. The external radiation hazard is controlled by the classic principles of exposure time, distance (the inverse square law), and shielding. The contamination hazard is easily controlled by use of protective gloves and clothing. Airborne contamination is only controllable by effective ventilation.

12.5.1. Effects of radiation

There are two types of radiation effect, which must be understood, as all are potentially involved in radioiodine therapy.

Stochastic effects

Here the probability of the effect occurring is assumed to be simply and proportionately related to dose, down to zero dose — for example, carcinogenesis and reasonable well understood, hereditary effects (i.e., those occurring in subsequent progeny of the exposed person and in turn their descendants) are yet to be proven in human population in general and certainly not documented for the types and amounts of radiation exposure involved in radioiodine therapy.

Deterministic effects (tissue reactions)

In this case there is a threshold dose, below which the particular effect does not occur. Above the threshold, however, the effect does occur, and the severity increases with dose. There is a range of different thresholds, as there are many deterministic effects which can occur. Examples are skin burns, epilation, radiation sickness and oedema.

12.6. Measurement of radiation

There are a number of methods for detection and measurement of radiation, and the selection depends on the application, as well as the cost. In particular, two types of instruments are required in radioiodine therapy — survey/contamination meters, and personnel monitors.

Survey meters are used to detect and measure the photon radiation levels — for example in measuring the radiation level emitted by the patient. They should also be useable for contamination monitoring by detection of either the photons or electrons emitted by ^{131}I . Personnel monitors are used to measure the radiation dose received by staff working with the patient.

For detection of the medium energy photons of ^{131}I , and their measurement to a reasonable degree of accuracy, a simple and relatively cheap device such as a Geiger counter can be used. This is a gas-filled detector which has a wide range, from individual radiation events, to reasonably large radiation fields. They can be calibrated to measure exposure or absorbed dose, and usually have an optional audible indicator, which is of great assistance when checking for contamination. Both can be calibrated in absorbed dose, or equivalent dose. A further factor can be used to estimate effective dose, if the approximate wearing position is known.

Personnel monitors must be small, light and robust. They must be able to measure photon dose, as well as give an indication of electron exposure. The two most common devices are the film badge and the thermoluminescent dosimeter (TLD). The film badge, as the name suggests, uses a special radiation-sensitive film to detect radiation, and is placed in a special holder with filters of different materials to assist the supplier to identify the energy and type of radiation detected. The minimum detectable dose is however somewhat high at about 200 microGray. TLD measures absorbed dose directly, and can be made into very small and lightweight badges. They have a lower minimum detectable dose (around 10-50 microGray). Unlike film badges, the detector is reusable. Both TLD and film dosimeters are worn for a period of between 4 and 12 weeks before being sent for evaluation.

There is another type of detector which may be used for short periods, for example in emergency situations. This is the electronic detector, which is often based on a miniaturized Geiger detector, but with a direct digital readout. The accumulated dose may be read at any time, and a dose rate alarm may be incorporated. All radioiodine facilities must have ready access to a survey/contamination meter, and staff working with the patients should have individual personnel monitoring.

12.7. Minimisation of radiation exposure

For a more detailed approach on rational, classification of people (patient, public, staff and carer) refer to ICRP and IAEA publications. For external radiation, there are three standard methods — time, distance and shielding. The *time* a person is exposed has a simple relationship to dose — double the time, double the dose. *Distance* is however different. A relationship known as the inverse square law, which applies for point sources, states that the dose or dose rate will be in inverse proportion to the square of the distance from the radiation source. For example, doubling the distance will reduce dose by $1/(2^2)$, or a factor of four. This means that the dose will rapidly decrease as distance from the source is increased. The reverse will also apply however, in that the dose will rapidly increase as distance is reduced. When the dose is not represented by a point source, but is distributed in a patient, the inverse square law only applies at larger distances (see 8.1.3). Distance is however a highly effective means of protection. *Shielding* is simply a matter of using radiation absorbers. Due to the relatively high photon energy from ^{131}I , fixed shielding in walls and other barriers is the only feasible safety measure. Normal lead gowns as worn by staff in radiology offer little protection.

12.8. Pre-treatment preparation

Radiation safety of thyroid therapy starts long before the radioiodine is administered. There are a few aspects which must be considered if a safe and effective treatment is to be achieved.

Pregnancy

As a rule, a pregnant woman should not be treated with a radioactive substance unless the radionuclide therapy is required to save her life: in that extremely rare event, the potential absorbed dose and risk to the foetus should be estimated and conveyed to the patient and the referring physician. Appropriate risk and benefit assessment must be before further considerations including terminating the pregnancy (<http://rpop.iaea.org>) and ICRP publications [12.7, 12.8].

The consequences can be that iodine will cross the placenta, and urinary radioiodine will irradiate the uterus. Patients should be warned as far in advance as possible not to become pregnant. At the time of admission for therapy, the patient must be asked if they are pregnant. Even if the answer is 'no', a pregnancy test is strongly recommended, if not mandatory. A reliable and sensitive pregnancy test is a serum or urinary beta-HCG (human chorionic gonadotrophin). It is very sensitive, but even this will not detect a pregnancy in the first day or so following conception. For this reason, many hospitals choose to perform two beta-HCG tests 24 hours or more apart. This should give a high degree of confidence in the pregnancy status of the patient. It is still possible that a pregnancy could still go undetected before the radioiodine is administered. If this happens, expert advice must be taken as to whether the pregnancy should be terminated. Continuation of the pregnancy is not normally advisable.

Babies and breast feeding

Breast feeding is absolutely contraindicated during, and for some time following, radioiodine therapy. If this is not done, the infant who is breast fed from a radioiodine treated patient, may become hypothyroid for whole life or be at high risk for subsequent thyroid cancer. A mother must be advised of this, and especially understand that her child will not be allowed to be with her during the treatment, and that breast feeding must cease prior to treatment, and not resume on discharge.

Incontinence

As will be discussed in more detail later, the main excretory pathway for radioiodine not taken up by thyroid tissue is the kidney and bladder. As a thyroid cancer patient has had the vast majority of thyroid tissue surgically removed, the urinary excretion of radioiodine can be in excess of 95% of the administered activity. This can constitute a serious radiation hazard. If the patient is known to be incontinent, arrangements should be made for urinary catheterisation for at least the critical period of the therapy (discussed later).

Future pregnancy

It is advisable to warn the patient before treatment of any precautions which might be suggested regarding future pregnancy. These are discussed in detail later.

General advice

Radioiodine therapy is not unpleasant in itself, but the patient's lack of thyroxine, their anxiety and the fact that they are to be effectively in isolation for a few days require explanation before admission. A little preparation can make the patient's stay happier, which means fewer radiation safety problems. Patient cooperation is vital to a safe and effective treatment, so it is important that they are kept as informed as possible about their disease and its treatment. An information sheet, provided to the patient at the time the therapy is arranged, can prevent many problems, and help the patient prepare for the treatment. It can cover many of the topics listed above, and inform them of what to expect once they come into hospital. In particular, the patient must be advised that they will be placed in a restricted access area (preferably single room), and may have limited visitors. In other words, they will be in semi-isolation for at least part of their hospital stay. They should also be advised to bring the minimum of personal items with them, as these can become contaminated by saliva or sweat during the treatment.

An example of a patient information sheet is shown in 12.12.

12.9. Treatment

12.9.1. Protocols and procedures

Careful preparation is essential. Many accidents in nuclear medicine can be traced to inadequate preparation, lack of protocols, or failing to follow existing protocols. In radioiodine therapy, the consequences of an accident can be severe. The first step in introducing radioiodine therapy should be the preparation of protocols. These should cover the entire treatment episode, from the request for treatment to post-discharge. Possible protocols required are:

- Request and ordering of radioiodine;
- Patient dose preparation and administration;
- Nursing procedures;
- Accident procedures;
- Discharge information.

Request and ordering

A significant radiation safety problem can occur at this early stage — as simple as confusion with units. Throughout the world, SI and non-SI units are in common and often in simultaneous use. The nuclear medicine department must standardize on one unit, preferably that in legal use in the country or that used by the supplier. If SI units are in use, and a request for treatment is received as 150 mCi for example, the patient dose must be converted to SI units immediately (in this case, 5.5 GBq), and the conversion checked. If a different unit is used by the supplier, again any conversion must be checked.

Case Study 1

A nuclear medicine technologist has to prepare two ^{131}I patient doses — one of 230 MBq (approximately 6 mCi) for an outpatient therapy for thyrotoxicosis, the other of 6 GBq for thyroid cancer inpatient therapy. The two patient doses are accidentally mixed up and the 6 GBq patient dose is given to the thyrotoxicosis patient. The cause is determined to be that

the dose calibrator was set to display mCi, and when the technologist saw ‘6’ on the display, assumed this meant 6 GBq. While the procedure was checked, it was by a student who had never worked in non-SI units. As a consequence, the thyroid of the thyrotoxic patient was ablated.

12.9.2. Form of radioiodine

^{131}I comes in two forms — a solution of labelled potassium iodide, and a gelatin capsule containing labelled sodium iodide on anhydrous disodium hydrogen phosphate. The choice of which form ^{131}I to use, is usually made after considering factors such as convenience, availability, cost and patient cooperation. Each has its own advantages and disadvantages, some of which are summarized in Table 12.4.

TABLE 12.4. AVAILABLE FORMS OF RADIOIODINE

	Advantages	Disadvantages
Liquid form	Cost Readily available	Easy to spill Volatile Can form droplets Difficult to use
Capsule form	Simple to administer Low contamination risk	Cost Must not be chewed Some bowel activity

If the liquid form is used, it will normally be supplied in a multidose injection vial. Administration to the patient involves some risk of contamination especially if using an open vial. Even if a flow/venting system is used (introduction of a needle and tubing through which the patient sucks up the radioactivity), there is still the risk of contamination, for example due to patient’s coughing. Liquid radioiodine is also volatile, with the subsequent risk to assisting staff of inhalation, and is easily transmitted through the skin. Capsules are very unlikely to cause a significant contamination hazard (although many will have some surface contamination). Chewing the capsule can however, lead to potential contamination similar to the liquid form.

12.9.3. Patient dose preparation and administration

Once the radioactivity is received in the nuclear medicine department, there are a number of steps which should be followed:

- Record the delivery — date, activity and form.
- When unpacking the radioactivity, wear gloves and check the packaging for contamination. Small (rarely, large) amounts of radioactivity can be found in any part of the packaging. The most likely, but not only, location is on the surfaces of the lead pot. Unpacking should take place in a fume hood to lessen the risks of airborne contamination.
- Measure and record the activity. Suppliers are not immune from mistakes, and there have been cases where the labelled activity is not what is delivered.

- Replace the radioactivity in the lead container, label the container and store in a safe place to await administration.

For patient dose administration, the nuclear medicine staff should have a trolley to transport the patient dose to the patient treatment room. This will carry not only the patient dose to be administered, but also the necessary aids — for example plastic cup, water, plastic forceps, metal tray with a lip (in case of spillage), warning signs, patient identification bracelet etc. Staff must wear disposable gloves and protective clothing such as a gown to absorb any spilt material. Only persons involved in the administration are to be present. If capsules are used for the patient dose delivery, special ventilation of radioiodine rooms is not required. However, if open liquids are administered, this must be done in a well-ventilated area. Only qualified staff should be involved in the radioiodine administration, and preferably include a nuclear medicine physician.

Before any attempt is made to administer the radioiodine, the patient MUST be positively identified.

The patient's name alone is not sufficient identification. Address and date of birth, and any other appropriate identification (such as medical record number) must also be used. The patient must also be asked if they understand the treatment. It is also advisable that the patient have an empty stomach at the time of administration. This speeds up the absorption of the radioiodine, lessens the radiation dose to the stomach, and minimizes the volume of any vomit. Once the patient has been correctly identified, patient dose administration may be done. The actual administration method will depend on the radioiodine form and preferred procedure. It is advisable that the whole procedure is documented, for example in the form of a checklist (see example in 10.14) This can also include a patient consent as shown in the example. If a liquid form of patient dose is to be used, the delivered radioiodine should be diluted with water to ensure that the maximum proportion of the radioactivity is actually given to the patient, and to reduce the activity of any droplets, should the patient cough during administration. Liquid administration carries the greatest potential hazards of contamination, and so the procedure used must be rigorous.

The patient should be asked to remove any dentures as these will become contaminated. The patient should drink the solution through a straw without removing the straw from the container or their mouth, until the administration is complete. The container should be refilled with water at least twice. This also has the effect of reducing the remnant activity in the straw and container. The patient should then be asked to drink a cup of water to remove oral activity. Capsules have far fewer problems, but the patient must be told to swallow the capsule, and not to chew it.

All steps in the administration process should be checked independently by a knowledgeable person to minimize the risk of errors. All measurements must be recorded.

Finally, the treatment room, and all items used in the administration, must be checked for contamination, and any necessary warning signs put in place (see later). Contaminated items must be either disposed of correctly and safely, or stored until sufficient radioactive decay has taken place.

Case Study 2

A 65 year old female patient, with early dementia is to be treated with a 6 GBq I¹³¹ capsule. Both she and the assisting nurse are warned that the capsule must not be chewed. The capsule is taken, as instructed, with water. Following swallowing, the patient's opened mouth is checked, and no capsule is seen. On a routine check the following day, extremely high activity is noted in the waste bin. It is subsequently determined that the patient did not swallow the capsule, but hid it in the back of her mouth, chewing it when the staff had left, during her meal. This transferred much of the activity to the disposable cutlery and crockery, and napkin. It was estimated that at least 50% of the patient dose did not reach the stomach.

12.9.4. Possible acute side-effects

There is a range of possible side-effects which may become apparent within a few hours or days of administration. The medical and nursing staff involved must be aware of these, and how to deal with them if necessary. The more likely side effects should also be explained to the patient.

Gastric

As patients already have very low levels of circulating thyroxine, they may feel generally unwell. When this is combined with anxiety related to the disease and treatment, and a low level of radiation sickness, it can lead to vomiting in the first 24 hours or so. This can be a serious radiation contamination problem, and should be avoided if at all possible. Many centres prescribe a prophylactic anti-emetic such as metoclopramide, administered shortly before the radioiodine is taken. In the great majority of cases this is sufficient to avoid vomiting. It is not however completely effective in all cases and local procedures must be prepared to deal with contaminated vomit. If vomiting occurs within the first few hours, the vomit can contain a high proportion of the administered activity, especially if a capsule was used.

Salivary glands

Again, the radiation can induce sialitis (or sialadenitis) — a relatively frequent acute effect — in the first day or two. It is best relieved by encouraging the patient to stimulate saliva production by chewing or sucking sweets. More rarely, there may be long term effects such as pain, dryness of mouth or even more rarely, development of nodules. These may only be related to high cumulative absorbed doses from multiple treatments.

Thyroid/Trachea

If there is a significant amount of thyroid tissue remaining, thyroiditis and associated oedema can occur, with possible tracheal compression. If it occurs, this can be a serious complication which must be dealt with quickly.

Bone marrow

It is possible for the patient to experience a transient fall in WBC and/or platelets. This is very rarely of any significance, and is usually not monitored.

12.9.5. Excretory pathways

Radioiodine will be excreted from the patient primarily by the kidneys, and consequently, the patient should be encouraged to drink freely to minimize dose to kidneys, bladder and gonads. Because of the lack of thyroid tissue, a great majority of the administered activity will appear in the urine. In most cases, 50-60% of the administered activity is excreted in the first 24 hours, and around 85% over a stay of 4-5 days [12.9]. This represents a significant potential for radioactive contamination. Measures for dealing with the excreted waste are discussed later.

The next most significant pathway is saliva. This will manifest in contamination of eating and drinking utensils, and pillow coverings (due to saliva excretion during sleep). Lesser pathways are sweat and faeces. The proportion of each (apart from urine) will vary widely, so it is best to assume that all forms of contamination are present, until proved otherwise.

12.9.6. Radiation monitoring and radiation safety precautions

The patient

The patient should be identified as receiving radioiodine treatment by means of a wristband, a clearly visible notice in their medical record, a sign on their bed, a sign on the bedroom door (see 6.6.4), or any combination of these. The wristband and medical record entry must include at least the radionuclide, activity administered, and date of administration. Figure 12.1 is an example of a patient identification wristband.



FIG. 12.1. Patient identification wristband.

From the time of administration to discharge, the radiation levels emitted by the patient must be regularly checked. Many countries have prescribed or derived limits of retained activity before discharge of the patient can occur. However, the ultimate purpose of such recommendations is that prescribed dose limits for members of the public and dose constraints for caregivers are not exceeded. They have wrongly been used as rigid levels without looking into other factors such as social, economic. Estimation of the retained activity level can be made by measuring the radiation level of the patient at a fixed distance (2 metres or greater to minimize errors) immediately after administration, and at other times. A simple Geiger counter, calibrated in dose rate, will be sufficient. As the radiation levels, and the administered activity are known, the retained activity can be roughly calculated.

For example, if dose rate at 2 metres after administration of 6 GBq = 0.09 mGy.hr⁻¹

Dose rate 4 days post-administration = 0.006 mGy.hr⁻¹

Retained activity = (0.006 × 6000)/0.09 = 400 MBq

The initial activity is of course effectively a point source in the stomach, while the later activity is in the neck or from metastatic deposits. This difference in geometry will introduce some error, but the method is suitable for routine use.

There should be a special record sheet kept with the patient's medical notes which contains details of the treatment, dose rate measurements, and approval for discharge and re-use of the bedroom. Figure 12.2 is an example of such a record.

The environment

As sweat and saliva are possible excretory pathways for radioiodine, monitoring of the patient's environment, at least at time of discharge, is necessary. The most likely contaminated objects will include bedding (especially pillows), toilet, telephone, drink containers and glasses, food waste and clothing. Monitoring can be performed with the same detector as for patient activity (as long as it has sufficient range), but it is advisable to have an audible indication of count rate. At the very least, the patient's room should be checked for contamination before the room is used again. The patient should of course be either absent, or at a significant distance from the detector during measurements.

Staff

Staff radiation dose must be minimized and measured. Minimising time spent with the patient, and remaining at a distance will provide good protection. There are cases however, when the patient requires a higher level of nursing care, and the staff will have to spend more time with, and closer to, the patient. In these cases it might be advisable to rotate staff regularly. Good and regular training of staff in all aspects of radioiodine therapy will also optimize their protection. Nursing care plans should also be designed with staff protection in mind. For example, for an otherwise well patient, observations of temperature and blood pressure can be performed daily at the most, or even less often if appropriate. Because of the potential for significant exposures, staff working in the facility should be monitored for radiation exposure with one of the devices mentioned earlier. Doses to nursing staff involved in the care of a patient in the 7 days following administration of 3.7 GBq I^{131} ranging from 0.16 mSv to 12.6 mSv (for a completely helpless patient) have been measured [12.10], depending on the level of nursing care required. However, if staffs are well trained, the care of the patients is rotated amongst available staff, and good procedures are put in place, staff doses can be held to quite low levels, less than 1 mSv per year. For temporary monitoring of special cases such as a high dependency patient, electronic dosimeters can be used to quickly and continuously assess dose.

The prime importance of distance as a radiation protection measure cannot be underestimated. Table 12.5 shows some typical radiation dose rates from the patient as a function of time, and Table 12.6 shows typical times spent by nursing staff in a normal working day with the patient related to the level of care required, and the distance from the patient.

TABLE 12.5. TYPICAL DOSE RATES AT 1 METRE FROM PATIENT ADMINISTERED 5.5 GBq

Day	Dose Rate (microGray/hour)
0	250
1	100
2	40
4	10



RADIOACTIVE IODINE-131 TREATMENT SHEET

Patient Name : _____

Medical Record Number : _____

Medical Officer : _____

Administered Activity : _____ GBq at (time) hrs on (date)

Dose Rate Measurements at 2 m

Date	Time	Dose Rate (microSieverts/hr)
<u>(admin. date)</u>	<u>(admin. time)</u>	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Patient discharge approved _____ (Signature)

_____ Date

Room safe for re-use _____ (Signature)

_____ Date

PATIENT MUST USE SPECIAL TOILET UNLESS OTHERWISE ADVISED

VISITORS ONLY TO BE ALLOWED WITH PERMISSION OF NURSING STAFF

NO PREGNANT WOMEN OR CHILDREN MAY VISIT PATIENT

FIG. 12.2. Treatment Record Sheet.

TABLE 12.6. TYPICAL TIMES SPENT BY A NURSING STAFF WITH A PATIENT PER WORKING DAY AS A FUNCTION OF PATIENT STATUS AND DISTANCE FROM THE PATIENT

Status	0.1 m	0.5 m	1 m
Very ill	1 hr	2 hr	30 min
Ill	20 min	90 min	60 min
Almost well	0	10 min	30 min
Well	0	5 min	10 min

Protection against contamination is efficiently provided by used of disposable gloves, and a gown.

As a general rule, there should be no sampling of patient's blood or urine during the hospital stay, due to the potential contamination of such samples, especially urine.

Case Study 3

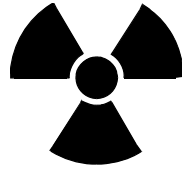
Nursing staff in the radioiodine treatment ward were regularly monitored with TLD badges, and the average monthly dose was 85 microSieverts. Suddenly, one nurse began to show monthly doses around 250 microSieverts on her badge. Her work practices were investigated and found to be no different to other staff, and in accordance with ward procedures. Eventually the medical physics staff noticed that she had a wrist watch pinned to her uniform, close to where she normally wore her TLD badge. The watch was investigated and found to have a high level of radium in the dial. Her normal watch had broken, and instead of buying a new one, she had used a watch she found at home. The radium-dial watch was removed, and her badge readings returned to normal. *Lesson* — an unexpected and unknown source of radiation was of more significance than routine work with radioiodine patients.

Visitors

Patients need not be placed in complete isolation, but care needs to be taken to control radiation exposure of visitors. A radiation warning sign must be placed on the bedroom or facility entrance. This should incorporate not only the trefoil symbol, but also a written warning of the radionuclide in use, and a statement that visitors are restricted and any other information felt necessary. Figure 12.3 is an example of a warning sign to be placed on the patient's door.

Pregnant women and children should be excluded from visiting. Adults should be encouraged to spend their visit at a distance of 1 metre or more from the patient, and in any case, the total daily visiting time per visitor should be limited. A visiting time limit of 15 minutes, calculated for 1.5 metres for example will provide sufficient protection in the case of an administered activity of up to 7 GBq. Although the patient's retained activity will rapidly decrease during their stay, it is preferable to use a standardized visiting restriction rather than to adjust it daily.

CAUTION RADIATION



THIS PATIENT IS BEING TREATED WITH 6 GBq OF IODINE-131
VISITORS ONLY ALLOWED WITH PERMISSION OF NURSING STAFF
MAXIMUM VISITING TIME = 15 MINUTES PER DAY
PREGNANT VISITORS AND CHILDREN MAY NOT ENTER

FIG. 12.3. Example of radiation warning sign for patient bedroom (figures in italics to be adjusted according to the patient).

12.9.7. Waste management

As mentioned above, there will be sources of radioactive contamination, which must be controlled. The main sources will be excreta and salivary contamination, with vomit as a further potential source. Some regulatory authorities require ‘delay and decay’ handling of urine, while others take the stance that levels of ^{131}I in sewage are not hazardous, particularly when the dilution factor is taken into account. Most hospitals discharge large volumes of liquid waste into the sewerage system, and the specific activity (concentration) of radioactive materials is very low as they are diluted by the large volume of non-radioactive fluids. In some instances however, where the sanitation infrastructure is not sophisticated, or in need of repair, the dilution factor cannot be relied upon.

‘Delay and decay’ is a generic form of waste management, in which the source is held in storage until sufficient radioactive decay has taken place to allow safe discharge into the general environment. However, ICRP in its recent report ICRP 94 [12.11] has clearly stated that with appropriate regulations, even without storage of urine, sewer disposal of excreta from patients diagnosed or treated with unsealed radionuclides has been shown to be well within both occupational and public radiation dose limits. It has been recommended in countries where the sewerage infrastructure is inadequate or may leak, creating an unsafe situation.

A good means of minimising spread of salivary contamination is to serve food on disposable plates, and ask the patient to use disposable utensils. These can be collected in the patient’s room and removed on a daily basis after monitoring. If contamination levels are high,

arrangements can be made for safe disposal. If the patient vomits, the resulting contamination can be widespread, requiring extensive decontamination. Planning for such an eventuality will minimise the consequences (emergency/accident procedures are discussed later). Disposal of vomit can pose a problem unless toilet disposal is possible.

Solid waste and contaminated materials can be dealt with by burial, incineration, or 'delay and decay'. The local regulatory authority must be consulted in the planning process.

12.9.8. Accident/emergency procedures

Possible eventualities which require planning include:

- Vomiting;
- Incontinence;
- Death;
- Respiratory or cardiac arrest.

Every hospital should prepare its own response procedures for the above, and there is obviously no single procedure which can be used. The following protocols and procedures however, adapted from a real hospital radiation safety manual, give a guide as to what should be considered.

Vomiting/contamination

Vomiting is an uncommon, but possible, occurrence in the first 48 hours or so following patient dose administration. Depending on the delay, the vomit may contain high levels of ^{131}I , and present a considerable contamination problem. Nursing and other ward staff must be trained to deal with the problem, as well as contamination from spilt urine and saliva. The nuclear medicine department must provide an emergency spill kit containing the basic materials required to deal with contamination. Contamination may also be found in toilet bowls, hand basins, room surfaces, items which the patient handles (including telephone), and personal items such as tissues [12.12]. Disposable items should be placed in a separate waste container for collection, measurement and appropriate disposal. Contaminated objects may need treatment to reduce radioactivity levels, or even storage for decay.

There should be staff in the hospital trained in basic decontamination procedures. The simple steps in decontamination are:

- Identification of the contaminated area;
- Isolation of the contamination to prevent spread;
- Removal of the contamination;
- Evaluation of the site after decontamination;
- Securing the contamination site if any radioactivity remains.

A basic decontamination kit should be kept near the patient's bedroom, to allow rapid and first response decontamination should it be necessary. The kit should contain as a minimum:

- Disposable gloves, gown and overshoes;
- Plastic bags (to contain waste);
- Absorbent paper towels;

- Small scrubbing brush;
- Radiation warning labels for waste bags or door;
- Decontaminant solution (detergent — stable sodium thiosulphate may be added).

If the skin of staff is contaminated, the affected area must be quickly and thoroughly washed with warm soapy water, and the area checked with a radiation monitor by the Radiation Protection Officer. Washing should be continued until the radiation level is less than about three times background level, or until it can be reduced no further. In any case of actual or suspected staff contamination, it is advisable to perform a check of thyroidal ^{131}I levels, as radioiodine can quickly pass through skin, and be taken up by the thyroid. It must also be recognized that iodine vapour arising from fluids is also a radiation hazard.

The following is a suggested form of information for ward nursing staff:

'Radioactive contamination'

As mentioned, most of the administered radioiodine not taken up by thyroid tissue is excreted by the urine in the 48 hours or so following administration. However, some is excreted by perspiration and saliva. For this reason, patients should be considered as a potential source of radiation contamination, especially during the first 48 hours following administration.

If nursing staff is to come into contact with the patient, bed linen, etc. while in the room, they must wear a gown and disposable gloves. Discarded gloves are to be placed in a nominated and marked contaminated waste bag. Further, the patient's meals must be served on disposable plates and utensils should also be disposable. Plates and all utensils should be placed in a plastic bag after use which should be kept in the room until checked for contamination. If safe, it may then be disposed of normally.

If the patient vomits, or urinates in the bed, it must be assumed, until proven otherwise, that the contamination is radioactive. During working hours the Radiation Protection Officer or, if not available, a member of the nuclear medicine department, must be called to assess the situation and supervise the cleaning up procedures.

If nursing staff are required to help they should be gowned and gloved, as before. The ward decontamination kit contains the materials required, including overshoes which should be worn if it suspected that there is any contaminated material on the floor. All soiled materials, gloves, and in this case the gown, should be placed in a separate and marked contaminated waste bag, sealed and labelled with a radioactive waste label and kept in the room until checked for radiation levels.

Case Study 4

A 34 year old male patient was explained about the procedure and possible side effects. The Radiation Protection Officer had prepared a contamination kit (containing basic materials for dealing with contamination, and waste storage bags), which was kept adjacent to the patient's room. Even with prophylactic anti-nausea medication, the patient vomited during the night. When in the morning the nursing staff came to check on the patient, it was found that the patient had cleaned up the contamination using contamination kit, placed all contaminated materials including gloves in a waste bag, labelled it and placed it in the shower recess in the bathroom!

Urinary incontinence

This is a special contamination issue because of the high radioactivity levels which can be encountered. As far as possible, patients should be screened for potential incontinence, and catheterised prior to treatment, and remain so until discharge, or for the first 48 hours of hospital stay at least. If possible, the catheter should be inserted 24 hours prior to radioiodine administration, to allow the patient to adjust, and for any problems to become apparent. The patient should be, as usual, encouraged to drink freely, and the staff should empty the catheter bag frequently to avoid a large accumulation of activity. Patients who are confined to their bed for other reasons, even if showing no signs of incontinence, should seriously be considered for catheterisation to avoid the close staff contact and potential for contamination involved in use of bedpans.

Cardiac or respiratory arrest

A life-threatening arrest can involve staff who will normally not be involved in radioiodine therapy. Particularly if such therapy is common, all medical and nursing staff who is involved in resuscitation should be aware of the potential problems. Again, what follows may be used as a guide.

'General procedures'

Resuscitation of patients containing radioactive material for therapeutic nuclear medicine poses some special problems. Please remember that the patient's welfare is the first concern. For the relatively short period of time involved, if the guidelines are followed, radiation exposure to staff will be very small and definitely not a cause for concern. Arrests in such patients are rare.

Patients treated with Iodine-131

Patients with thyrotoxicosis or thyroid carcinoma are treated with oral Iodine-131, which is absorbed through the gut over a period of some hours. These patients contain a wide range of radionuclide activity, in general thyrotoxicosis patients contain less than carcinoma patients. However, the patient dose, the time since administration, and the thyroid tissue uptake are the factors which most determine actual radionuclide remaining. Till few hours following administration, the gut may contain a significant amount of radioactive material, rapidly decreasing with time. Further, radionuclide not taken up by thyroid tissue is predominantly excreted by urine over two days or more.

Action to be taken

- Do NOT apply direct mouth-to-mouth resuscitation, but use either a resuscitation mask such as Air Viva or Concord to avoid contamination.
- Staff involved in resuscitation must wear disposable gloves.
- Materials which have come into direct contact with the patient should be, as far as is practicable, kept to one side for contamination checking, and possible decontamination. This particularly applies to airways, masks, endotracheal tubes etc.
- Notify the department of nuclear medicine immediately.

As intubation, catheterisation or a nasogastric tube may be necessary, staff is to be gowned and wear gloves when handling the patient. Attempt to contain any urine, gastric contents or

any other body fluids by means of absorbent pads, and hold the pads in a contaminated waste bag for contamination checking. Similarly any suction bottles or urine bags used must not be discarded until checked.

Examination of staff involved in resuscitation or handling of the patient

Staff who have been directly involved with the patient will need, for their own safety and peace of mind, to be assessed as to the potential radiation exposure, however small. This will include best possible estimation of radiation exposure and, if there is any suspicion that radioiodine has been ingested, administration of Lugol's iodine as soon as possible to block thyroid uptake of any absorbed contaminant and subsequent measurement of any thyroidal accumulation of Iodine-131.

Transfer to intensive care or coronary care

If transfer is required, the fact that the patient may still contain radioactive material is not to interfere with the 'management'.

Case Study 5

A male patient being treated with radioiodine suffered a respiratory arrest. The nearest doctor immediately attended the patient, and revived him using an external mask. The doctor called for assistance, and when the arrest team arrived, she left the room. She was some two months pregnant at the time, but followed the above principles. Subsequent monitoring and simulation showed that she had not ingested any ^{131}I , and her external exposure was very low. The patient survived, and the pregnancy and baby were normal.

Death of the patient

There are two particular problems which may arise from the death of a radioiodine therapy patient. Firstly, the hazards to staff involved in handling the body, and secondly, the possibility of an autopsy examination must be considered. Advice must be sought from the local regulatory authority. Local cultural practices may complicate the problem, and each country should decide what its requirements are, and the local Radiation Protection Officer must be involved in their implementation. In view of varying cultural issues involved, the figures stated in following paragraphs should be taken as typical ones practiced in some countries and are not consensus derived by IAEA. Readers are referred to review of guidelines from number of countries as given in ICRP Publication 94. Summary of guidelines have also been provided on IAEA web site at <http://rpop.iaea.org> or more specifically at: http://rpop.iaea.org/RPoP/RPoP/Content/InformationFor/HealthProfessionals/3_NuclearMedicine/TNM_AccIncidents.htm

The following is a suggested protocol for medical and nursing staff.

A number of special precautions must be taken in the case of the death of a patient who contains radioactive material for therapeutic purposes. Procedures for handling the body can be divided into two: Ward/Medical Staff Procedures, and Mortuary Procedures.

Ward procedures

The Radiation Protection Officer and the department supervising the patient's treatment must be informed as soon as possible after death. All such patients will have a yellow 'Radioactive

Material' wrist identification band, in addition to the regular wrist band stating that radioactive material is present in the patient. **This is not to be removed on death.** Only a minimum of laying out procedures should be attempted (e.g. replacement of false teeth) and the sheet in which the body is wrapped should be labelled with a yellow 'radioactive material' label, used in conjunction with the routine mortuary labels which will be available in the ward. The label should be clearly visible to all those handling the body. The body should be removed as soon as possible after death from the ward, without attempting to remove any of the radioactive material, and placed in, if possible, the centre section of the body storage refrigerator. This is to minimize any radiation exposure to staff who may be working the mortuary.

Mortuary procedures — general principles

Exposure of individuals to radiations emitted by radioactive materials retained in or on a corpse can be reduced by adopting any or all of the following precautions:

- Working expeditiously to reduce the time of exposure.
- Working at a distance from radioactive material rather than working unnecessarily close to it.
- Working, where necessary, behind adequate shielding.
- The Radiation protection officer (RPO) must be consulted on the radiation problems likely to be met in making an autopsy or in the disposal of the body.
- When a body is to be released for direct burial without embalming or post-mortem no special precautions are normally required, but recommendations by the RPO shall be observed.

Autopsies — general comments

There is a general feeling that if a corpse contains less than 200 MBq ¹³¹I the procedures normally observed during autopsy may be adequate for the examination unless such examinations are carried out frequently. The pathologist must be informed of the presence of the radioisotope, and the precautions required. If, however, a corpse contains activity in excess of this, the pathologist must be informed of the radiation levels likely to be encountered and of the hazards involved. The methods employed and the precautions adopted should be chosen accordingly. Occasionally corpses are assigned to medical schools for dissection or are to be transported overseas. Any hazards to persons involved in these operations or the need for compliance with international transport regulations depend on several factors relating to the nature of the radioactive sources. In most instances the issue is resolved by keeping the corpse in appropriate cold storage until a number of half-lives of radioactive decay have passed. The RPO shall be consulted for guidance. The thyroid region should be excised before the examination proceeds and removed from the work area. It may later be disposed of with the body after consultation with the RPO. Body fluids should be drained off, using suitable equipment, before the examination proceeds. These fluids may be often safely disposed of via the sewerage system as instructed by the RPO. The equipment used during the autopsy should later be decontaminated by thorough rinsing in a detergent solution (preferably with a soluble iodine agent added) followed by washing in running water.

Precautions to be taken in disposal of a corpse containing radioactive materials

No special precautions are normally required in the direct burial, without embalming or post-mortem, of corpses containing residual therapeutic doses of radioiodine, but recommendations by the hospital RPO shall be observed. No special precautions are necessary for the embalming or burial of corpses containing not more than 600 MBq ^{131}I . Corpses containing activities greater than this should not normally be embalmed, but if there are special reasons for doing so in a particular case, the embalmer must first consult the Radiation Protection Officer. In many countries no special precautions are necessary for the cremation of corpses containing not more than 1000 MBq ^{131}I . The possibility that special circumstances may arise in the transport of a corpse containing radioactive materials should be considered in relation to the requirements of local legislation covering the transport of radioactive materials.

The disappearing patient

If the patient suffers dementia, or is very uncooperative, he/she could leave the bedroom undetected and thus become a potential public health hazard. If this is at all likely, a radiation alarm mounted outside the bedroom could be considered, which would sound an alarm if the patient left the room. Other preventative measures could be to site the treatment bedroom within sight of the nursing station, but in particular to educate the patient that it is imperative they do not leave the room without permission. If the patient has indeed disappeared, then a rapid and strenuous effort must be made to find them, particularly in the 24 hours following patient dose administration.

12.9.9. Discharge

As mentioned earlier, there are various criteria used to determine when the patient may be discharged. There are effectively three types: an absolute retained activity, an absolute external dose rate from the patient, and a retained activity based on the potential radiation exposure to family members and the public.

The International Basic Safety Standards (BSS) for radiation protection (IAEA, 1996) include the maximum activity for patients to be discharged from a hospital. The BSS indicates that a patient shall not be discharged from hospital before the activity of radioactive substances in the body falls below the level specified in Schedule III, Table III–VI. The guidance level for iodine-131 given is 1100 MBq, although there is a footnote that a level of 400 MBq is used in some countries as a measure of good practice. The IAEA indicated that, following radionuclide therapy, patients may not be discharged until the remaining activity subsides to an acceptable level, and that the regulatory authority should set the level according to international standards (specifically BSS, Schedule III, Table III–VI), taking local conditions and the potential exposure of other members of the patient's households into account. Additionally, activity in the patient should be estimated or measured prior to discharge, and the result should be recorded. The patients should be given written and verbal instructions of necessary precautions for protection of relatives and others with whom they may come in contact. Special precautions may be needed for the elderly or children.

ICRP Publication 94 provides comprehensive guidance and following paragraphs have been taken from the same. The cornerstone of release criteria are dose limits for the public and dose constraints for the family and caregivers. In spite of this there is a wide variation in criteria used to decide whether to release patients. At present, the two general forms of release criteria

are those based on individual situations and projected doses to other persons or alternatively retained activity criterion (usually based on conservative assumptions).

Since lifestyle habits differ around the world and even within one country, a single model for release criteria would not be appropriate optimization. It is recommended that there be release of patients based on family situation (rather than retained activity and worst case scenario) and that in order to discourage “nuclear therapy tourism”. It is also recommended that when there are many contiguous countries, a uniform or similar approach to releasing patients be developed.

The decision to hospitalize or release a patient should be individually determined and should not be linked only to residual activity in the patient but should take into account many factors including the patient’s pattern of contact with other persons, the patient’s wishes, occupational and public exposures, family considerations, cost and environmental factors.

ICRP recommendations do not explicitly require that patients be hospitalized after therapy with high activities of radiopharmaceuticals but rather that public dose limits and dose constraints for others is observed. This should be followed by optimization. Some authorities require hospitalization of patients based on only retained activity without other important factors including appropriate optimization being taken into account.

Recent publications indicate that assumptions used by some authorities to require hospitalization may overestimate potential doses to the public and caregivers.

The next important action at discharge is advice to the patient. This should be in writing, and cover:

- Contact with family members and members of the public;
- Sanitation;
- Contact with pregnant women and young children.

A sample of the advice is given in the information sheet in 10.3 Sample Patient Information Leaflet.

Advice regarding contact with other persons is largely dependent on the local retained activity at discharge, however a simple rule is for the patient to remain in general at arm’s length for the first week. This (as well as many others of these recommendations) may of course be difficult to implement in some cultures. This does not mean though that can be ignored.

A particular problem is when a female patient has very young children. As thyroid cancer often strikes younger females, this is relatively common. Breast feeding **MUST CEASE** immediately the treatment is commenced and no attempt made to recommence. It is extremely important that the patient understands this, as the damage which could result to the infant from ingestion of radioactive breast milk would be very serious. It is very difficult for a mother of infants to avoid holding her child — the advice will have to be firm, but recognize that brief periods (at least) of holding will happen unless the child can be cared for by someone else. At the risk of alarming the mother, the monitor used to perform regular radiation levels can also be used to demonstrate the rapid rise of dose rate as distance is decreased, in accordance with the inverse square law.

Further information regarding the well-being of the patient after treatment is discussed later.

12.9.10. Safety of family members following discharge

Although the BSS [12.4] recommends a 1 mSv annual effective dose limit to a member of the public, this does not apply to ‘comforters of patients’, which includes family members (Schedule II, para. II-9). The dose to these persons should however, be constrained so that it is unlikely that the dose will exceed 5 mSv. The concept of a dose constraint of a few mSv per episode for caregivers and family has often been inappropriately interpreted as a rigid annual dose limit. Also the stipulated figure of 5 mSv has mistakenly been taken as dose per year rather than dose constraint per episode. It is clarified that infants and young children as well as casual visitors be excluded from the dose constraint and be limited to the public dose limit [12.13, 12.14, 12.15].

12.9.11. Return to work

Discharge to the home, as mentioned above, is based on a higher potential radiation exposure to family members than for the general public. It is necessary to consider separately when the patient may return to normal life outside the home. For example an extra half-life decay may be indicated if the patient’s work environment involves long periods of close contact with other persons. Each case should be taken on its merits after a discussion with the patient prior to discharge.

12.9.12. Discharge to a non-home environment

Some patients may return not to home, but to a residential care facility such as a nursing home, and require high levels of care. The discharge criteria may be the same as above, but only if the facility staff are aware of, and accept, the minor radiation exposure risk involved.

12.10. Long term advice

Up until now issues relating to treatment and the discharge of the patient have been considered. There are potential long term effects on the patient, which should be discussed with the patient, or which the patient’s doctor should be aware of. Although there is still some uncertainty about the actual risks involved, none can be completely ignored.

12.10.1. Future pregnancy

In recent years there has been a change in the approach towards having pregnancy following radioiodine treatment. Treatment is not regarded as must for not having pregnancy in future [12.16]. However, more relevant is whether the treated patient is male or female. The only adverse effect noted in female patients was a small increase in risk of miscarriage if conception occurred within a year of treatment. This however, may not be due to the radioiodine, but to the abnormal thyroid hormone status during this time. There are significant differences in spermatogenesis and oogenesis, and in the case of male patients, the germ cells are potentially affected by the treatment. However, as they have a short lifetime, a common practice is to advise the patient that they should not attempt pregnancy for at least 6 months following treatment.

12.10.2. Carcinogenesis

Although ionising radiation is known to be carcinogenic or leukaemogenic, studies have shown no strong relationships between radioiodine treatment and subsequent cancer. Individual studies have reported either little or small excess risks. For example Edmonds

[12.17] reports a small excess increase in deaths from cancer of the bladder (0.4 per 10⁴ patient Gray years — PGY) and from leukaemia (4.9 per 10⁴ PGY). Other studies [12.18, 12.19] showed no significant links to cancers or leukaemia. Patients could be advised that, the radiation treatment may not completely exclude future cancer or leukaemia but these are very unlikely to occur.

12.10.3. Other complications

Other potential radiation-related complications studied [12.17] were reduction in fertility, and impaired pulmonary function. Neither was observed.

12.11. Design of facilities

The radioiodine patient should not be treated in the general hospital ward, but in an appropriately designed area. The following section describes the type of design criteria which should be used for such a treatment area.

12.11.1. Physical design

Location

There is no reason why a radioiodine facility cannot be located in a general ward area, however the location and design both need consideration. The facility should be away from public areas to allow control of access (including from any balconies), and because the patients usually require low levels of nursing care, does not have to be close to the nurses' station. Use of external walls can reduce radiation shielding requirements, especially if the facility is above ground level. If at ground level, public access to external areas should also be controlled.

Design and finish

Ideally, the radioiodine facility should have not only a patient bedroom (or more than one), but also a dedicated shower/toilet for each room and a waste storage/dose preparation area. The location and orientation of the patient's bed should allow for easy observation by nursing staff with optimum safety particularly from a distance.

The finish of the rooms must allow for easy decontamination in case of accidental spillage of contaminated fluids, etc. This means that:

- All floors must have a smooth, waterproof, continuous finish (such as vinyl), with coving to the walls;
- The bathroom floor must also be of a non-slip type;
- Walls must be finished with a washable material such as gloss paint;
- Furniture must be similarly waterproof and washable, i.e. no cloth surfaces;
- The door to the bedroom should have a glass viewing window, and be at least 2 metres from the bed;
- Waste storage bins must have removable plastic liners so the contents do not have to be handled.

As the patient is to be kept in semi-isolation for the period of their stay in hospital, they should have all the necessary facilities such as telephone and television available to them in their room.

If capsules are used for the dose delivery, special ventilation of radioiodine rooms is not required. However, if open liquids are administered, this must be done in a well-ventilated area.

Radiation shielding

As the activity level can be significant, and the photon energy of ^{131}I is reasonably high, shielding of a radioiodine facility is important. This is particularly so if the facility adjoins other patient, staff or public areas. Shielding design is not difficult, and will take into account the following issues:

- Source term;
- The maximum expected activity;
- The maximum expected number of patients per year in the room being considered;
- The expected effective half-life;
- The expected length of hospital stay;
- The expected radiation dose rate from the patient;
- The distances to, and occupancies of, adjacent accessible areas;
- The target design dose in accessible areas (including any constraints required by the local regulatory authority);
- Attenuation of possible shielding materials for ^{131}I photons.

The following uses an example to illustrate the principles of shielding design.

Source term

Current practice is for a typical administered activity of around 6 GBq, with a range of 2 GBq to 7.5 GBq. For the example, take 6 GBq.

Assume the effective half-life is 1 day (24 hours), and a hospital stay of 3 days (72 hours). The integrated activity is then 9 GBq-days, which means for calculation purposes that there is a continuous activity in the patient of 3 GBq during their stay.

Let us also assume that the facility is expected to take an average of one patient per week.

Dose rate from patient

There is a range of dose rate data published for ^{131}I , from 51 to 76 $\mu\text{Sv.GBq}^{-1} \text{ hr}^{-1}$ at 1 metre. Note that the dose rate from a patient will usually be less due to absorption in their body, and has been measured at around 45 $\mu\text{Sv.GBq}^{-1} \text{ hr}^{-1}$ at 1 metre, so this value should be used.

For a point source, normally the inverse square law is used to correct the dose rate for distance, but in the case of a source distributed in the body, this does not apply for short distances (up to 3 metres). A good approximation is that the dose rate falls according to $(\text{distance})^{-1.5}$.

Distances to calculation points, and occupancies

These can be measured from plans, and should be taken from where the boundary of where the patient is expected to spend their time in the bedroom, to 0.5 metre on the far side of each wall or barrier.

The occupancy is an estimation of the fraction of time an area is expected to be occupied. These are usually quite conservative, and include values of 1 for offices, 0.25 for corridors and 0.06 for toilets.

Target or design dose

This is the dose in mSv per week, which the shielding will be expected to limit radiation dose. For areas occupied by radiation workers this is the occupational dose limit specified in the BSS [12.4] of 20 mSv per year averaged over five consecutive years, and for the public, 1 mSv in a year. An additional dose constraint should also be considered [12.4]. For example, a constraint of 0.2 is often used for medical radiation workers.

Attenuation data for shielding materials

There is a large amount of data on the shielding properties of standard materials such as lead and steel. The shielding designer must however, be aware that attenuation for other materials such as bricks or cement blocks can vary greatly. It is assumed lead is to be used as the shielding material. The half value thickness for ^{131}I photons in lead is 3 mm [12.1].

Sample calculation

Let us assume that the room next to the patient's bedroom is an office (occupancy = 1), and that the distance from the patient is 2.5 metres.

The distance-corrected dose over a 3 day stay per patient (see source term above) is therefore given by:

$$\begin{aligned} & (3 \text{ GBq} \times 3 \text{ days} \times 24 \text{ hours} \times 50 \text{ patients} \times 45 \text{ microSv.GBq}^{-1} \text{ hr}^{-1}) / 2.5^{1.5} \text{ microSv/year} \\ & = 122\,950 \text{ microSv/year} \\ & = 123 \text{ mSv/year} \end{aligned}$$

If the target dose is 1 mSv per year, then the required attenuation is $1/123 = 0.008$. This equates to 7 half value thicknesses, or approximately 27 mm lead.

This is only an example — each facility should be designed according to the criteria and assumptions required by the local regulatory authority.

Shielding construction

Normally, shielding need only extend to 2100 mm above the floor level. There should however be no gaps or holes in the shielding, and doors may need to be shielded.

It is highly recommended that installation of shielding be supervised, and be tested before the facility is used.

12.11.2. Radioactive human waste management

The waste that is of concern is the urine, which may or may not be associated with faecal excretion. The urine has a high specific activity at the beginning of the treatment, and low at the time of discharge. The faeces may have some radioactive content, especially if a capsule is used, but is not regarded as a major problem. This has led to two approaches to the management of radioactive urine — to simply allow excretion into the normal sewage system, or to follow the principle of ‘delay and decay’ by use of storage tanks. In any case, the patient should flush the toilet after each use, and possible twice, to minimize contamination of the toilet bowl.

Normal discharge

This relies entirely on the dilution of the ^{131}I by the normal waste discharge from the hospital to a point where the specific activity is acceptable to the regulatory authority. In some cases, the assumed discharge, and subsequent dilution in the sewage main, means that there are no restrictions on discharge from radioiodine therapy patients. If unrestricted discharge is not permitted, in some cases a calculation of the actual discharge and dilution may permit a limited number of patients and total activity to be discharged without treatment of the effluent [12.20]. It is quite important that the local regulatory authority is consulted, and the necessary approvals gained before unrestricted discharge is commenced. If a restricted discharge is possible, the calculations must be made to the satisfaction of the regulatory authority.

Delay and decay

Unrestricted discharge is however, not permitted in a number of countries. For example the Canadian limit for discharge of ^{131}I through the sewer is 370 Bq.L^{-1} based on a yearly average [12.21]. If a hospital treated 50 patients per year with an average dose of 6 GBq, and 90% excretion is assumed, the total discharge would be $2.7 \times 10^{11} \text{ Bq}$. To reach the required specific activity limit would require this to be diluted into 7.3×10^8 litres. A large hospital might discharge at a rate of only around 10^7 litres per year. Hence the waste cannot be simply discharged, and some form of treatment must be used. The only treatment of radioactive sewage practical is to store it temporarily in tanks, for a period long enough for the activity to decay to a level where it may be discharged. With appropriate regulations, even without storage of urine, sewer disposal of excreta from patients diagnosed or treated with unsealed radionuclides has been shown to be well within both occupational and public radiation dose limits [ICRP Publication 94]. Delay tanks can be expensive and complicated, adding significantly to the cost of a radioiodine treatment facility, possibility of increased exposure to maintenance staff and with further possibility of accidental exposures in the event of calamity.

The details of a delay tank design are beyond the scope of this report, however they must take account of:

- The total excreted activity per year (usually the total activity administered is used);
- The facility waste volume discharged per year;
- The allowed maximum activity concentration in sewage allowed by the regulatory authority;
- The volume of, and frequency of, the flush in the patient’s toilet.

From the above, the required decay time can be calculated, and thus the volume of the storage tank. Two tanks at least will be involved — one filling whilst the other is decaying. The

resultant tank volume is usually in the range 2000 to 4000 litres, with decay periods around 4-8 weeks. Owing to the absorption of the ^{131}I photons in water, there is normally little special shielding required, as long as the tanks are in a controlled access area. There will however, be the need for control and monitoring systems to allow the tanks to be operated and checked remotely, and with appropriate emergency systems. Single decay tanks may be used, but these require a large volume, and longer decay period to allow the permitted average specific activity. A special case of a single tank system used occasionally is what might be called a 'trickle tank'. In principle, this is a large volume tank with the discharge point at the opposite end from the entry. The assumption is that by the time a particular litre of effluent migrates to the discharge point, it has undergone sufficient decay.

See Annex II - Sample Patient Information Sheet.

See Annex III - Sample Dose Administration Record.

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13. ROLE OF EXTERNAL BEAM RADIOTHERAPY

13.1. Radiotherapy

The successful treatment of thyroid cancer depends on the histology of the cancer, its size, presence of metastasis. The external beam radiation therapy (EBRT) can be given locally to the neck or to isolated metastases where there has been insufficient ^{131}I uptake for an adequate therapeutic effect [13.1]. EBRT is effective for locoregional control and certain metastatic foci in thyroid carcinoma. It can be used alone or in combination with ^{131}I . Definitive EBRT requires careful treatment planning because doses as high as 70 Gy are required and administered over a 7.5 week period. By comparison, thyroid lymphoma requires only about 45 Gy over 4.5 to 5 weeks [13.2].

Although EBRT can be performed using either a linear accelerator or cobalt teletherapy machines, the sharper beam and the larger field sizes, along with the better availability of photons and electrons favour the use of the linear accelerator over cobalt-60 in treating thyroid cancers.

Indications for EBRT of thyroid cancer are shown in Table 13.1, but more generally include:

- Bulky tumour (e.g. mediastinal disease) large enough that it is uncontrollable by ^{131}I alone.
- Residual bulky tumour in the central neck, trachea, and oesophageal area or cervical nodal regions after thyroid surgery and removal of malignant cervical adenopathy that may not be controlled by ^{131}I alone.
- Skeletal metastasis
 - uptake of ^{131}I is insufficient
 - impending pathologic fracture, regardless of the degree of ^{131}I uptake
- Brain metastases.
- Metastases (lung) if symptomatic or when other treatment methods have been unsuccessful.
- Relief of pressure symptoms occurring in vital areas caused by soft tissue masses.
- Superior vena cava syndrome.
- Continually recurring thyroid cancer regardless of ^{131}I uptake.
- Recurrent or metastatic thyroid cancer occurring after maximal ^{131}I therapy.
- In sequence or conjunction with chemotherapy, particularly in anaplastic cancer.
- Inoperable locally advanced thyroid cancer: EBRT as palliation.

General indications of EBRT according to histological classification (3-4) are given in Table 13.1.

TABLE 13.1. GENERAL INDICATIONS FOR EBRT ACCORDING TO HISTOLOGICAL CLASSIFICATION

Tumour	Stage	Treatment
Papillary or Follicular	Invasive, <45 years age Invasive, or possible residual >45 years age Recurrent, any age, first ¹³¹ I repeatedly Isolated lesion in the bone	External irradiation to thyroid bed after ¹³¹ I
Medullary	Stage III Abnormal or increasing tumour burden Recurrent tumour Isolated metastasis	External irradiation to thyroid bed. To mantle field To thyroid bed To symptomatic area
Lymphoma	All	External irradiation to thyroid bed.
Anaplastic	All	External irradiation to thyroid bed.
Persistent and Recurrent Disease	1. Local recurrence 2. Bone metastases	External irradiation if ¹³¹ I is ineffective. External irradiation to symptomatic areas.

13.2. Differentiated thyroid cancer

The role of external beam radiation therapy (EBRT) in differentiated thyroid cancer has been reviewed in the presence of gross residual disease after attempted surgical excision. Retrospective series have reported local control is possible with EBRT. If used in addition to ¹³¹I, there is a role for adjuvant EBRT in differentiated thyroid cancer, it is only in patients in whom there is a high risk of relapse in the thyroid bed. There is evidence to suggest that EBRT can improve the local relapse-free rate in selected patients, such as those over the age of 45 years, those with microscopic residual disease, or extensive extra-thyroidal invasion [13.5].

The previous widespread belief that these cancers are ‘radio-resistant’ is now less evident as more reports on the beneficial result of EBRT in papillary and follicular cancer are published [13.6]. Several authors have retrospectively reviewed their experience with EBRT and suggested an improved local control and/or survival benefit [13.7]. Simpson and Carruthers showed that patients with surgically narrow or microscopically positive margins may benefit from the addition of EBRT in moderate doses [13.8]. This study combined 13 Canadian institutions using EBRT in patients with high-risk fractures, including those with extra-thyroidal invasion, high grade malignancy and older age group. Local control significantly improved both papillary and follicular cancer. Overall survival in papillary thyroid cancer significantly improved with and without use of ¹³¹I therapy. Tubiana and co-workers retrospectively reviewed 539 patients with thyroid cancer, where 97 received post-operative EBRT and some received ¹³¹I also [13.9]. EBRT was given for prophylactic treatment and for macroscopic residual disease. Overall, the risk of local recurrence was significantly reduced with the addition of EBRT.

Benker and associates showed no survival benefit with addition of EBRT in 932 patients of differentiated thyroid cancer [13.10]. On subset analysis, patients of age more than 40 years, and those with T-3 and T-4 disease experienced improved survival which was statistical significance.

A Belgian study of 94 patients with microscopic and macroscopic residual disease or nodal involvement with extracapsular extension showed that despite poorer prognostic factors in the EBRT group (38 of whom had EBRT) [13.11], only one local failure was reported compared with 14 in those patients who only received ^{131}I therapy. In this study, toxicity due to EBRT was low, with doses at 55 Gy to the treatment volume.

A study of 1599 patients from the MD Anderson Cancer Hospital in the USA showed that 113 patients who received EBRT failed to report any advantage [13.12]. However, a selection bias where the EBRT group had poorer prognostic factors, more advanced disease, less surgery than the rest of the population influenced the findings.

The overall data published from these studies indicates that although the definitive role of EBRT for differentiated thyroid cancer remains controversial, there appears to be a select population of patients having microscopic or presumed microscopic residual cancer, who may benefit from the addition of local EBRT. These cancers slowly regress after radiation therapy often requiring more than a year to obtain the maximum response, analogous to the situation when ^{131}I is used to treat gross disease. Radiation therapy is particularly useful for treating the thyroid bed when residual microscopic disease is suspected. When gross disease is present, either local, regional or as a solitary distant metastasis, EBRT should be administered in addition to the functioning tumour, since ^{131}I alone may not eradicate gross tumour masses completely or permanently. Under ideal clinical circumstances, however, this will be a rare requirement, as patients should have adequate surgical removal of gross thyroid tissue followed by radioiodine treatment. Palliative EBRT is also useful in alleviating bone pain, and preventing pathologic fractures or superior vena cava compression in some patients [13.6].

13.3. Medullary thyroid cancer

At present, surgery is the most important treatment for medullary thyroid cancer (MTC). Radiotherapy and chemotherapy play a marginal role in advanced MTC [13.13, 13.14]. As with papillary and follicular cancers, MTC responds slowly following radiotherapy. There is no place for small volume irradiation in the primary treatment of this tumour. Radiotherapy should always consist of modified mantle technique [13.6]. In MTC and undifferentiated thyroid cancer, once the cancer spreads to distant organs, there is virtually no efficacious therapy. However, growing knowledge of the specific genes involved in thyroidal oncogenesis may contribute to the future development of more effective treatment modalities [13.9].

13.4. Anaplastic thyroid cancer

Since EBRT is a localized form of treatment, the impact of radiation must be assessed in terms of local control within the irradiated volume. However, local control and cure rate are not synonymous, and despite local control, the majority of patients die of disseminated disease [13.6].

13.5. Lymphoma

Combined chemotherapy and irradiation are effective in thyroid lymphoma [13.6]. Consequently, total thyroidectomy should no longer be considered the first-line treatment. Furthermore, there is evidence to suggest that the most efficacious therapy is systemic chemotherapy in combination with EBRT for local control. Debulking surgery has a role to provide relief from acute airway obstruction [13.15]. Radiotherapeutic management of clinical stages I and II primary thyroid lymphoma should include treatment of the neck, axillae and mediastinum to a dose of approximately 4000 cGy using a continuous course technique [13.16].

13.6. Miscellaneous malignancy

For rare variants such as squamous cell cancer, post-surgical EBRT may also have a role. Other histologic varieties, including Hurtle cell carcinoma are characterized by advanced disease at the time of diagnosis and by may be unresponsive to treatment. Except where there is a clear-cut palliative benefit often, these malignancies go untreated because the acute complications may exceed any benefit produced by surgery, irradiation or chemotherapy.

13.7. Squeal of radiotherapy

Acute reactions in treating very large volume include:

- Mucositis requiring supportive treatment including intravenous fluid, soft diet and analgesic;
- Monilial superinfection — requiring antifungal antibiotics.;
- Fatigue and lassitude — usually subsiding within 1-4 weeks after completion of EBRT;
- Haematopoietic depression — rarely prevents completion of EBRT but the patient's blood count should be monitored regularly.

Late reactions are infrequent and include:

- Lhermitte's syndrome — consists of sensation felt like an electric shock down the back and into the legs on flexing the head briskly. This appears 2-3 months after EBRT, and most often subsides over 9-12 months, but may persist for up to 24-30 months.
- Transverse radiation myelopathy — manifests within 9-15 months if spinal cord tolerance doses are exceeded.
- Radiation skin atrophy — minimal with high energy radiation.
- Dryness of the mucous membranes within treatment volume.
- Secondary malignancies (mainly skin lesions) are rarely seen.

13.8. Other radiotherapy modalities

- Intra-operative radiation therapy (IORT) has been used for poorly differentiated non-anaplastic thyroid carcinoma. IORT is administered after tumour surgery (4-10 Gy) and combined with post-operative percutaneous irradiation [13.16].
- A similar potential role exists for brachytherapy.

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14. ROLE OF CHEMOTHERAPY

14.1. Introduction

The role of chemotherapy in differentiated thyroid carcinoma is limited, unlike other solid malignancies where it is widely used as an adjuvant therapy. Most differentiated thyroid carcinomas can be successfully treated by the combination of surgery, radioiodine and L-thyroxine suppressive therapy. The role of chemotherapy is restricted to the treatment of i) locally advanced or metastatic nonfunctioning or non-iodine concentrating differentiated thyroid cancer, ii) anaplastic thyroid cancers, and iii) advanced metastatic medullary thyroid cancers. Chemotherapeutic agents are used either as monotherapy or in combination with more than one drug. In order to increase the effectiveness and decrease the toxicity of drugs, they are also used along with other treatment modalities (multimodal treatment), particularly with external beam radiotherapy. Addition of chemotherapy to surgery and external radiotherapy is reported to improve the survival in medullary thyroid cancer [14.1-14.3].

14.2. Differentiated thyroid cancer

Chemotherapy is rarely used for management of differentiated thyroid cancers and hence the experience is limited. Only relatively few patients have received chemotherapy for locally advanced carcinoma or metastatic disease. Most results are published as case reports or small series. Therefore, the value of chemotherapy is difficult to ascertain. The first chemotherapeutic agent to be used to treat differentiated thyroid cancers was bleomycin. The response rate with bleomycin monotherapy varied from 0-50% [14.4-14.9] but severe side effects such as lung toxicity have stopped bleomycin from more extensive use. Another drug used more widely with some success, probably most effective mono-chemotherapeutic agent used so far, was Doxorubicin. The overall response rate reported in 83 patients of differentiated thyroid cancers from eight studies was 38.5% (21-80%) [14.5, 14.10-14.16]. However, the response was partial and of brief duration. Further, Doxorubicin therapy is associated with cardiotoxicity occurring at doses of 550 mg/m² and above. Other chemotherapeutic agents used were methyl-chloroethyl-cyclohexyl-nitrosourea, Rubidazone, peptochemiol, Aclarubicin, Mitoxantrone, endoxan and Pepliomycin [14.17-14.19]. These drugs were either ineffective or had very limited, non-lasting effects on the tumour suppression. Usually, a patient who responds to the first drug given is likely to respond to a second drug and that patients who do not respond to the first will rarely do so to other drugs.

Since a single agent was not effective and associated with side effects, multi-drug therapy using various combination of drugs and dosages have been tested. Doxorubicin (60 mg/m²) along with Cisplatin [14.11, 14.16, 14.20], or 5-Fluorouracil 500 mg/m²/day, cyclophosphamide 300 mg/m²/day and etoposide 16 mg/m²/day [14.11] have been used. The results have been disappointing and average response rate of multiple-agent chemotherapy appears to be only slightly better than that of doxorubicin single-agent chemotherapy.

14.3. Anaplastic cancer

In contrast to the indolent differentiated type, anaplastic giant cell thyroid carcinoma is one of the most aggressive tumours in humans. Mean survival without treatment is 3 to 6 months, and single modality treatment does not seem to change the survival time [14.21]. In the management of anaplastic cancer, chemotherapy is more frequently used as these tumours do not concentrate ¹³¹I and are more often unresectable.

In the early 1970s, combinations of chemotherapy (actinomycin D, bleomycin, and cyclophosphamide) and radiotherapy were reported to give promising results [14.2, 14.3]. However, in large series of 84 patients, this combination was not effective [14.22]. Doxorubicin monotherapy alone or in combination with external radiotherapy has resulted in a response rate varying between 10-22% [14.5, 14.10, 14.15, 14.23]. Treatment with Bleomycin showed a partial response rate of 25% in primary tumours and 50% in lymph node metastases [14.8]. Aclarubicin was found to be ineffective with a brief partial response of only 14% [14.18]. Methotrexate (5 mg/day, for 5 days) treatment with external radiotherapy (40 Gy in divided doses over 5-6 weeks) in five patients has been reported to result in complete regression of primary tumour. However, patients had severe side effects and they died due to local tumour recurrence and pulmonary metastases within 5-13 months [14.24]. As this combination carried severe side effects, methotrexate was replaced by BCF (bleomycin 5 mg/day, cyclophosphamide 200 mg/day, 5-fluorouracil 500 mg every second day). This combination was found to be less toxic. Seven of nine patients had complete or partial remission. Further, BCF was replaced with doxorubicin, as the hyperfractionated BCF regimen had side effects that were fairly severe. Sixteen patients were treated with pre- and postoperative doxorubicin and hyperfractionated radiotherapy. Of these, five patients had a complete remission, and two patients survived more than 2 years [14.25].

Shimaoka and associates [14.16] used a combination of doxorubicin 60 mg/m² and cisplatin 40 mg/m² in 18 patients and compared the results with that obtained in 21 patients treated with doxorubicin alone. They found the response rate to be significantly better in combined drug therapy as compared to monotherapy. However, Williams, et al. [14.20] failed to observe any response in 7 patients of anaplastic thyroid cancer using the same combination of drugs. Recently, Biganzoli, et al. [14.26] used epirubicin and carboplatin to treat 11 patients of anaplastic thyroid cancer. Although, they found complete response in 18%, which lasted for more than 1 year, 73% of cases had a progressive disease indicating the ineffectiveness of the treatment. Kim and Leeper [14.27] treated 19 patients with anaplastic thyroid cancer with a combined regimen consisting of a weekly administration of adriamycin 10 mg/m² before hyper-fractionated radiotherapy (1.6 Gy twice daily for 3 days per week to a total dose of 57.6 Gy in 40 days) and reported an initial tumour response rate of 84%. The local tumour control rate at two years was 68%. However, most of their patients developed distant metastases and died (median survival 1 year). In 1980, Simpson, et al. [14.28] reported complete response in six and partial response in seven of 14 patients treated with single-drug chemotherapy (doxorubicin) and hyper-fractionated radiotherapy.

A higher success rate (4 with complete response and 5 with partial response in a total of 10 evaluable cases) has been reported using multimodal treatment with doxorubicin (60 mg/m²) and cisplatin (90 mg/m²) along with a split course of external radiotherapy [14.29]. This regimen was effective in longer survival and local control, but was ineffective in controlling distal metastases. Moreover, it had severe side effects. Tennvall, et al. [14.30] treated 33 patients with hyperfractionated radiotherapy (30 Gy, either 1 or 1.6 Gy twice daily in 30 fractions for 3 weeks), followed by adriamycin 20 mg/m² intravenously weekly, surgery and post-operative 16 Gy/16 fractions. They obtained complete local remission in 48% and four patients survived for more than 2 years with no evidence of disease. More recently, for treatment of 37 patients Kobayashi, et al. [14.31] used external radiotherapy (conventional 50 Gy or hyperfractionated radiotherapy to a total dose of 30 Gy) along with chemotherapeutic agents (adriamycin 30 mg/m², mitomycin and cyclophosphamide before 1984 and doxorubicin 30 mg/m² and/or cisplatin 70 mg/m² after 1983) and showed the benefit of combined chemo-radiotherapy in eradicating the residual tumour and control of local

recurrence. Combinations of cisplatin, adriamycin, etoposide, pepliomycin, and G-CSF repeated every 3 weeks, with local external radiotherapy, wherever required, showed a partial response in 40% of the patients with a mean survival of 7-11 months [14.32]. Busnardo, et al. [14.33] investigated the role of multimodality treatment in 39 consecutive patients with a histologically or cytologically proven anaplastic thyroid carcinoma from 1992 to 1999. A total of 16 patients (Group 1) were treated with total thyroidectomy, radiotherapy and chemotherapy with adriamycin and bleomycin in various order. Nine patients with distant metastases at diagnosis (Group 2) received chemotherapy; one of them had a disappearance of lung metastases and was then treated by total thyroidectomy and further chemotherapy. Four complete responses were seen in patients from Group 1, and 1 from Group 2. Median survival rate was 11 months for Group 1 and 5.7 months for Group 2. Only a few patients responded to chemotherapy, confirming that anaplastic thyroid carcinoma is often resistant to anticancer drugs. They concluded that aggressive and appropriate combinations of radiotherapy, total thyroidectomy and chemotherapy may provide some benefit in patients with anaplastic thyroid carcinoma. Preoperative chemotherapy and radiotherapy may enhance surgical resectability of the primary tumour.

Santini, et al. [14.34] evaluated whether increasing the metabolic rate of thyroid cancer cells by TSH stimulation might result in higher response rate to chemotherapy. A combination of carboplatin and epirubicin was administered at 4- to 6-week intervals for six courses in fourteen patients with poorly differentiated thyroid carcinoma and nonfunctioning diffuse lung metastases. TSH stimulation was achieved by reduction of the daily dose of L-thyroxine resulting in mild hypothyroidism (eight patients) or by administration of recombinant human TSH (six patients). One patient had a complete remission. Five patients had partial remission, and seven patients had disease stabilization. One patient progressed to death. The overall rate of positive responses was 37% that rose to 81% when patients with stable disease were included. Serum thyroglobulin after chemotherapy declined more than 50% in six patients, with respect to basal levels. They did not find any difference in the response rate between exogenous or endogenous TSH stimulation. They concluded that the response rate of poorly differentiated thyroid cancer to chemotherapy could be favourable and promising with TSH stimulation.

The appropriate treatment strategy of anaplastic thyroid cancer is yet to be evolved. No definite form of therapy has been recommended. However, in view of the aggressive nature of the disease, multimodal treatment including aggressive surgery, RT and high dose combination CT could offer a better survival.

14.4. Medullary thyroid cancer

Medullary thyroid cancer is a neoplasm of calcitonin secreting parafollicular C-cells of the thyroid gland. It occurs in sporadic form in about 80% of the cases while 20% could be familial belonging to either MEN IIa, MEN IIb or non-MEN familial medullary thyroid cancer. Medullary thyroid carcinoma may have an indolent behaviour and patients with distant metastases do well. However, the disease could be aggressive and needs prompt treatment. As this cancer does not accumulate radioiodine, these patients are left with only option of chemotherapy with or without radiotherapy in cases of disseminated disease.

Reports on the use of chemotherapy in medullary thyroid cancer are limited to a small number of cases and at times is a single case report. These limitations make the interpretation of results difficult. Earlier studies, using single agents have shown controversial results. The reported response rate with doxorubicin varied between 0-66% [14.5, 14.8, 14.11, 14.15,

14.16, 14.23, 14.35-14.38], with cisplatin 0% [14.11, 14.37] and etoposide 50% [14.39]. The other chemotherapeutic agents, such as methotrexate, 5-FU and carmustine have not been found effective [14.40-14.41].

The combination of doxorubicin and cisplatin showed response rate varying between 0-33% [14.16, 14.42]. In a single case report Sridhar, et al. [14.43] observed a partial response with this combination. In a single case treated with dacarbazine 250 mg/m² per day for 5 days and 5-FU 450 mg/m² for 5 days, Petturson [14.38] reported a complete response. Using the same combination, Orlandi, et al. [14.44] treated five cases of advanced metastatic medullary thyroid cancer. Although, there was not a single complete response, there were three partial responses lasting for 9, 10 and 18 months. This combination appears to be promising, as there was less drug toxicity. Scherubl, et al. [14.45] used doxorubicin (50 mg/m²), cisplatin (60 mg/m²) and vindesine (3 mg/m²) in 10 patients and reported only 1 case (10%) with a partial response. Wu, et al. [14.46] treated 7 patients with advanced metastatic medullary thyroid cancer with cyclophosphamide (750 mg/m²), vincristine (1.4 mg/m²) and dacarbazine (600 mg/m²) daily for 2 days in each cycle every 3 weeks. There was no complete response either in terms of tumour size reduction or decrease in the levels of tumour markers. Two patients had partial biochemical response and reduction in tumour size; one had partial biochemical response with stable tumour size, while three had progressive disease. This combination was well tolerated with lower toxicity. Another variation in the combination of drugs and the protocol in 20 patients was alternating therapies with dacarbazine (200 mg/m²) and 5-FU (400 mg/m² i.v. daily for 5 days), and 3 weeks later, streptozocin (500 mg/m² for 5 days) and 5-FU (400 mg/m² i.v. daily for 5 days) [14.47]. The response was partial regression of tumours in three patients (at 11, 9 and 3 months) and stabilization of the disease in 11 patients. Drug toxicity was moderate and the quality of life improved. Yet another combination of doxorubicin (45-70 mg/m²), imidazole carboxamide (600-800 mg/m²), vincristine (2 mg) and cyclophosphamide (600-750 mg/m²) has been tried. The courses were repeated at 3 weekly intervals. Four responding patients were on therapy for 2, 2, 8, 10 months. There was progressive improvement in three patients and one patient had progressive disease [14.48].

Complete response has not been observed in any of the above mentioned regimens. Hence although there is no hope of a complete response, it appears that single or combination drug regimes can in a small number of subjects induce a partial response or stabilize disease for some months. There is not enough data to indicate whether the partial response is transient or long lasting.

14.5. Conclusion

The response to chemotherapy in patients with advanced differentiated thyroid carcinoma is not encouraging. Doxorubicin, cisplatin, and etoposide alone or in combination are the drugs currently considered effective. However, side effects may be severe and chemotherapy cannot as yet be routinely recommended. Chemotherapy in combination with external radiotherapy should be tried in cases of anaplastic thyroid cancer and chemotherapy remains the only alternative, though not very effective, in cases of aggressive and widespread medullary thyroid cancer.

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15. POST SURGICAL IMAGING EVALUATION

Despite being labelled as one of the most curable neoplasms, differentiated carcinoma of the thyroid (DTC) has a tendency of 5-20% to develop local or regional recurrences, and 5-10% to develop distant metastases, generally in the first 5-years of follow-up, but sometimes after many years [15.1]. The post surgical management of DTC consists of ablation of remnant thyroid tissue with Iodine-131 (^{131}I) and suppression of endogenous TSH with life-long thyroxine replacement, supplemented with regular thyroglobulin (Tg) assays and periodic imaging to detect possible recurrent or metastatic disease for further treatment with ^{131}I . The success of this management structure is highly dependent on the bulk of thyroid tissue left behind after thyroidectomy and the effectiveness of ablation. Total thyroidectomy is known to minimize recurrence rate and improve survival, but will additionally improve effectiveness of Tg assay by eliminating normal Tg production, and enhance the sensitivity of ^{131}I whole-body scan (WBS) by keeping competitive uptake of residual thyroid tissue to the minimum.

15.1. Imaging with ^{131}I

WBS remains by far the most cost-effective and widely used imaging method for follow-up of patients with DTC. It has favourable features that include low cost and easy availability, physiological uptake by thyroid and DTC cells and a gamma emission that is far from ideal but adequate for imaging. Its disadvantages include relatively low specificity and sensitivity, its tendency to induce stunning and the need for intensive patient preparation including withdrawal of thyroxine for at least 3-4 weeks and adopting a strict iodine-free diet that may not appeal to all patients. When uptake by residual or recurrent tumour is documented, it can be assumed that the tumour is amenable to treatment with a subsequent therapy dose of ^{131}I (Fig. 15.1). However, the issue of stunning has thrown doubt on the effectiveness of an immediate therapy dose following a diagnostic scan.

15.2. Limitations of ^{131}I WBS

15.2.1. *Low sensitivity*

Since the introduction of Tg assessment as a true tumour marker for DTC in the early 80s, comparative studies have shown its superiority over ^{131}I WBS in detecting recurrent or metastatic disease. In a study by Ronga, et al. [15.2] the sensitivity of ^{131}I WBS was 48% compared to 96% for Tg. Others have shown variable sensitivities but the most optimistic is probably not higher than 80%.

The low sensitivity of ^{131}I WBS can result from one or more of the following:

- Saturation of sodium-iodide symporter (NIS) by iodine rich diet or use of contrast media;
- Inadequate TSH elevation mostly due to non-compliance;
- Metastasis too small to be detected;
- Loss of ability to take up ^{131}I possibly due to de-differentiation of tumour cells as a result of an acquired mutation of NIS.

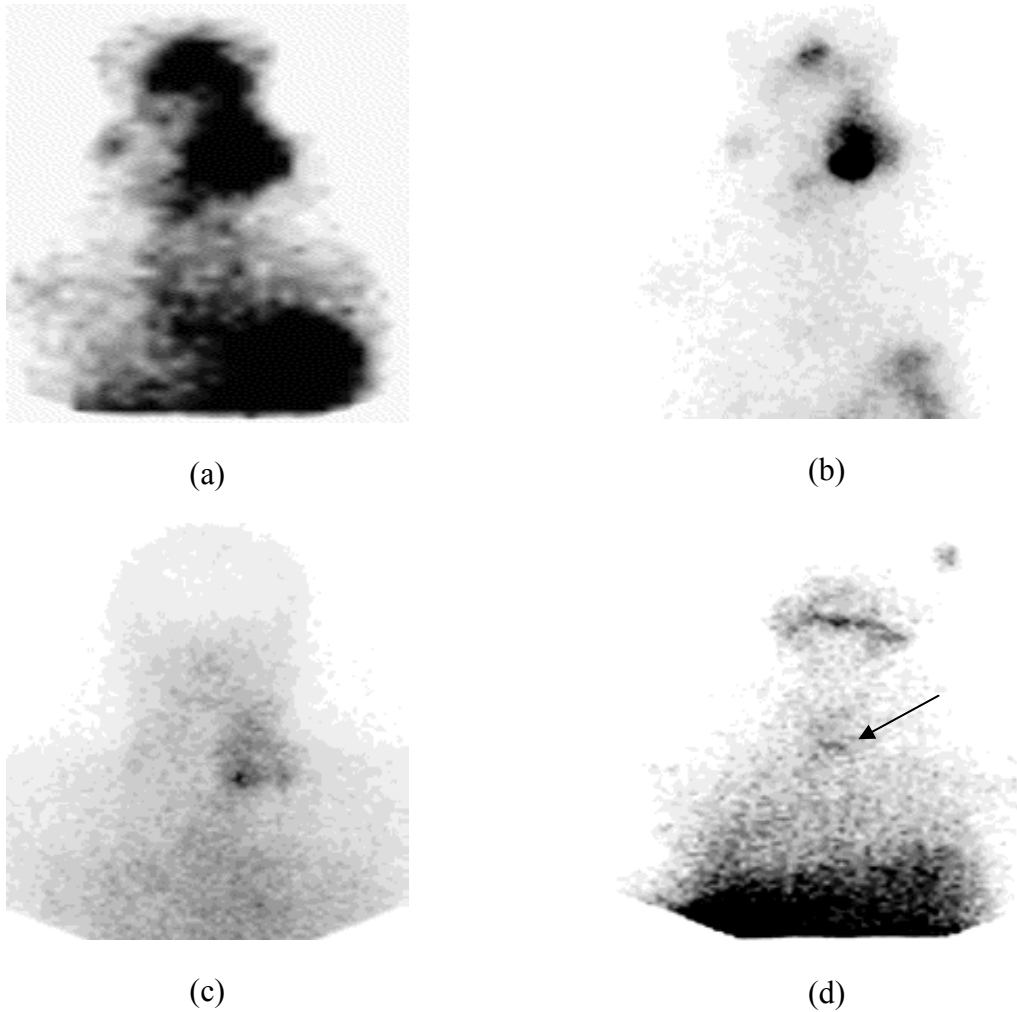


FIG. 15.1. Effect of surgery and ^{131}I repeat therapy doses on a locally invasive follicular carcinoma of the thyroid in a 16 year old girl. (a): post-ablation scan showing extensive residual disease; (b): diagnostic scan 4 months later showing more localized tumour; (c): WBS 3 months after 5.5 GBq (150 mCi) ^{131}I therapy dose still showing some residual disease; (d): diagnostic scan 4 months after 2nd surgery and 3rd therapy dose showing complete resolution. Note uptake in the thymus (arrow) confirmed with CT.

Measures to overcome these difficulties include strict patient preparation, the use of recombinant human TSH (rhTSH), improving image quality and resolution by administering higher ^{131}I doses [15.3], and the use of retinoic acid for re-differentiation of unresponsive tumours. However, in clinical practice, an alternative imaging is usually employed.

15.2.2. Low specificity

Acquisition errors, artifacts, physiologic distribution and non-thyroidal pathologic uptake of ^{131}I constitute the majority of false positive results. A list of possible causes of a false positive scan is shown in Table 15.1. It is prudent to keep a comprehensive and updated list of these conditions to aid in the interpretation of scans [15.4]. Correlation with ultrasound, computed tomography and other imaging modalities can be helpful.

TABLE 15.1. CAUSES OF FALSE POSITIVE ^{131}I WBS

Head & neck

Thymus, dacryocystitis, chronic sinusitis, artificial eye, wig

Pulmonary

Tracheostomy, inflammatory disease, carcinoma

GIT

Meckel's diverticulum, gastric adenocarcinoma, constipation

GUT

Poor renal function, cysts, ectopic kidney, cystadenoma, hydrocele

CVS

Pectus excavatum

CNS

Meningioma

Miscellaneous

Body secretion, skin burns, psoriasis, lactating breast

15.2.3. Stunning

Stunning is the term currently used to explain the phenomenon of failure of DTC to take up therapy dose given shortly after a diagnostic ^{131}I scan. There are conflicting reports of how often and with what dose of ^{131}I this can take place. The likelihood of stunning has somewhat altered long established imaging protocols and, in some institutions, has abolished pre-ablation diagnostic scans. Using small doses of ^{131}I may reduce the risk, though stunning has been reported with 74 and 185 MBq (2 and 5 mCi) ^{131}I [15.5-6]. One of the possible causes of stunning may relate to variable levels of TSH which can be overcome by the use of rhTSH. Other measures include postponement of therapy for weeks/months following a diagnostic scan or the use of ^{123}I (Fig. 15.2) or other imaging for diagnosis.

15.2.4. De-differentiation of DTC

Throughout the long term survival of patients with DTC, loss of differentiation is noted in one third of patients resulting in loss of thyroid specific function and increased tumour grading and severity. As a consequence to this, lesser Tg production and higher rate of false negative ^{131}I WBS will be noted.

Retinoic acids regulate growth and differentiation of normal epithelial tissue. They have been employed in anticancer treatment and showed positive effects in haematopoietic and various epithelial tumours. Experimental data with follicular thyroid tumour cells showed strong evidence of induction of differentiated cell function and antiproliferative effects [15.7]. The clinical use of retinoic acid can reverse de-differentiation of DTC and improve diagnostic and therapeutic potential of ^{131}I . Simon, et al. [15.8] used 13-cis-retinoic acid in a dose of 1.5 mg/kg/d for 5 weeks in 50 patients with DTC and noted an increase in ^{131}I uptake in 21 patients. An overall response, evaluated by changes in Tg production, ^{131}I uptake and tumour regression, was noted in 38%.

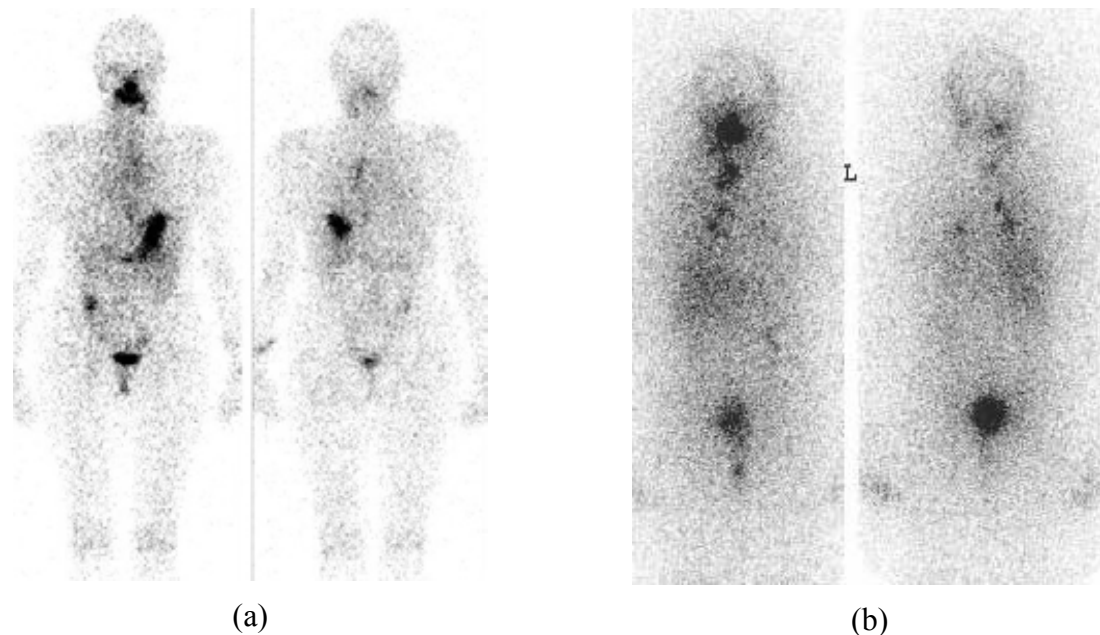


FIG. 15.2. Anterior and posterior diagnostic ^{123}I whole-body scan (a) and ^{131}I post therapy scan (b) in a 56-year-old female with clinically recurrent DTC associated with high Tg. The ^{123}I scan was done to avoid stunning. Note the higher uptake and wider distribution of metastasis on the post therapy scan.

15.3. Alternative imaging to ^{131}I

The combination of regular Tg assays and ^{131}I WBS has an estimated sensitivity and specificity of 97% and 100%, respectively [15.9]. However, current practice suggests that regular Tg assay on its own is adequate, and that ^{131}I WBS is only indicated when the former starts to rise. In this setting, ^{131}I WBS may fail to show recurrent or metastatic lesion(s) and the resulting ‘Tg positive — ^{131}I negative’ situation necessitates the use of one or more alternative radiopharmaceutical imaging supplemented with cross sectional radiology (CT, MRI, high resolution US) if and when necessary (Fig. 15.3). Contrast CT is to be strongly avoided if a therapy dose is planned. Some authors suggest a ‘blind’ therapy with 3.7GBq (100 mCi) ^{131}I in all Tg positive ^{131}I - negative cases and express doubt on the value of non-iodine imaging [15.10-12]. However, pre-treatment imaging is valuable in these circumstances to document the site(s) of residual or recurrent disease for future follow up and to assist in the management e.g. by opting for surgical resection if the lesion demonstrates radiobiological resistance to radioiodine and/or is localized and amenable to surgery.

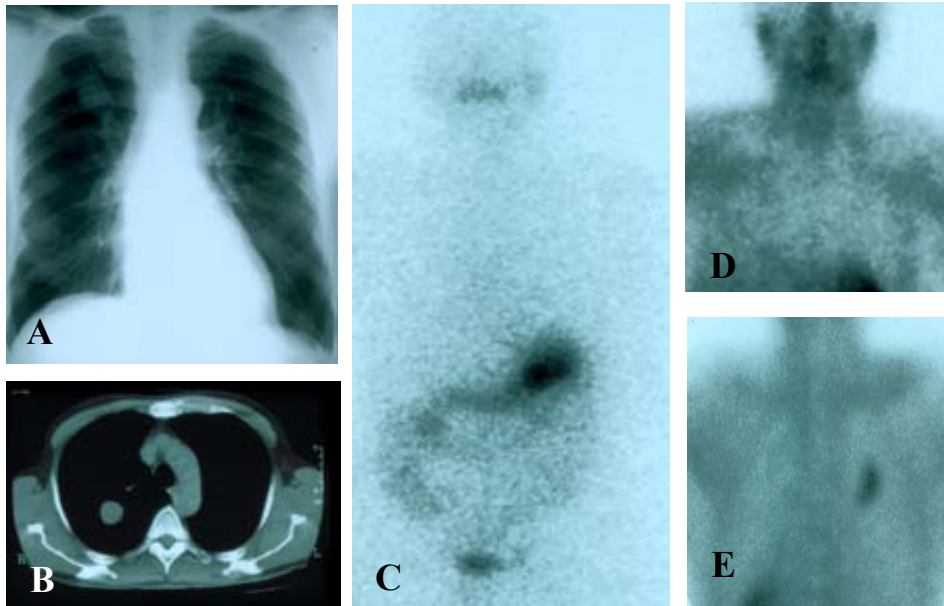


FIG. 15.3. Alternative imaging in DTC. A: A 52-year-old male with follicular carcinoma of the thyroid presented with rising Tg and RUL shadow (arrow) on CXR; B: CT scan confirmed presence of a well-defined rounded mass in the same area thought to be a benign haematoma; C: whole-body¹³¹I scan was negative; D: ²⁰¹Tl scan; E: ^{99m}Tc-MIBI (posterior view) demonstrated uptake in the lesion that was shown on biopsy to be a solitary metastatic disease.

Since early reports describing the utility of Thallium-201 (²⁰¹Tl) in detecting metastatic disease of DTC that were negative with ¹³¹I WBS [15.13], continuous efforts were made to search for the ideal radiopharmaceutical to complement or replace ¹³¹I in this respect. In addition to ²⁰¹Tl, Technetium-99m labelled radiopharmaceuticals such as ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin and ^{99m}Tc-MDP as well as Indium-111 labelled somatostatin receptor imaging (¹¹¹I-octreotide) and positron emission tomography with ¹⁸Fluorodeoxyglucose (FDG-PET) were used. A literature search spanning the last two decades reveals a wealth of publications that examines the individual roles of these radiopharmaceuticals and compares each against one or more others. A careful reading of these data suggests the following:

- A great proportion of studies relates to ^{99m}Tc-MIBI. Almeida-Filho, et al. [15.14] evaluated 99 patients with DTC, while on suppressive thyroxine treatment, with whole-body ^{99m}Tc-MIBI and compared the results with, using Tg as a gold standard. They found whole-body ^{99m}Tc-MIBI to be concordant with Tg in 96% and discordant in 4% of cases. Others recommend a combination of ^{99m}Tc-MIBI and neck US as a first line investigation in Tg positive — negative cases [15.15] and confirm high sensitivity for metastatic disease but lower sensitivity in detecting remnant thyroid tissue and lung metastases [15.16-17].
- Similar results were found with ²⁰¹Tl and ^{99m}Tc-tetrofosmin. In general, ^{99m}Tc labelled radiopharmaceuticals have better resolution than ²⁰¹Tl but head to head comparison between ^{99m}Tc-MIBI and ²⁰¹Tl showed very similar results with sensitivity of 53%, high specificity of 100% and an overall accuracy of 69% for both [15.18]. This comparative study employed planar images that missed residual cancer in high cervical lymph nodes adjacent to salivary gland activity, in small nodes of <1 cm deep in the neck or chest, and diffuse pulmonary micro-metastases. The sensitivity could have improved by tomographic acquisition, which is the current recommended procedure. A similar

comparative study between ^{201}Tl and $^{99\text{m}}\text{Tc}$ -tetrofosmin [15.19] revealed identical sensitivity of 79.4% in detecting metastatic lesions compared to 67.6% for ^{131}I . However, sensitivity for detecting lung metastasis were equally lower at 68.8%.

- Imaging with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -tetrofosmin was similar to that with $^{99\text{m}}\text{Tc}$ -MIBI in showing reduced sensitivity for detecting thyroid remnants but higher sensitivity in metastatic disease. However, some studies have shown good results with ^{201}Tl in the pre-ablative states. Carril, et al. [15.20] found at least one lesion that was ^{131}I negative but ^{201}Tl positive in 31 patients (15 pre-ablative and 16 post-ablative) out of a cohort of 116 patients with DTC. When discordant results were analysed, ^{201}Tl positive — ^{131}I negative lesions were more likely to be associated with high Tg levels, while ^{131}I positive - ^{201}Tl negative lesions were associated with normal Tg levels. This agrees with the observation made by Maxon [15.21] that tumour foci that concentrate either ^{201}Tl or ^{18}F FDG intensely with little or no ^{131}I uptake, behave more aggressively than those concentrating ^{131}I avidly. In general, imaging with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -tetrofosmin showed no difference in sensitivity when patients were on or off thyroxine replacement therapy [15.22].
- When comparative studies between the above mentioned radiopharmaceuticals were performed, the obtained results were not always concordant between them or with ^{131}I WBS. Similar discordance was found with Tg assays and clinical data. This meant that some lesions were only detected by ^{131}I WBS and/or Tg assay. This applies to imaging with ^{123}I (Fig. 15.2) and ^{18}F FDG and confirms the complementary role of alternative imaging [15.23].
- There is limited experience with ^{111}In -octreotide [15.24] and $^{99\text{m}}\text{Tc}$ -MDP [15.25], but the available data suggest lower specificity and confirm their role in complementing rather than replacing ^{131}I WBS.
- There is an increasing role for whole-body ^{18}F FDG-PET. In a recent multicenter study [15.26], 222 patients with DTC had ^{18}F FDG-PET, ^{131}I , ^{201}Tl or $^{99\text{m}}\text{Tc}$ -MIBI whole body scans. The results were evaluated against an overall clinical and biochemical assessment and showed ^{18}F FDG-PET to have an overall sensitivity and specificity of 75% and 90%, respectively. However, it demonstrated 85% sensitivity for patients with negative. Sensitivity and specificity for ^{201}Tl or $^{99\text{m}}\text{Tc}$ -MIBI were 53% and 92%, respectively for both. The high sensitivity of ^{18}F FDG-PET has prompted a suggestion that it should be the first line investigation in Tg positive — negative cases [15.27], but others stress on its role as complementary to ^{131}I WBS [15.28-29] particularly when taking into consideration its high cost and limited availability [15.24].
- Non-iodine imaging does not require withdrawal of thyroxine and is attractive to patients who loathe the disabling features of hypothyroidism. However, recent data has shown that using rhTSH enhances the diagnostic features of ^{18}F FDG-PET [15.30]. It remains to be seen whether imaging under rhTSH stimulation can have a similar effect on other alternative imaging.
- Despite the fact that alternative radiopharmaceutical have different mechanisms of uptake to each other and to that of, a positive scan with one of the formers followed by a therapy dose with, may lead to successful therapeutic effect and diagnostic visualisation and sometimes detection of extra lesions (Fig. 15.2) as does blind therapy based on elevated Tg on its own [15.10].

15.4. Summary

Combined whole-body ^{131}I imaging and Tg assay remain the most cost-effective and widely available method for post-surgical imaging and management of patients with DTC. When ^{123}I is available, it may replace ^{131}I to reduce the incidence of stunning. A major obstacle in the use of ^{131}I for diagnosis and treatment of DTC is de-differentiation that may be responsive to retinoic acid.

Alternative non-iodine imaging is increasingly being used for 'Tg positive — negative' cases employing ^{201}Tl , $^{99\text{m}}\text{Tc}$ -MIBI and $^{99\text{m}}\text{Tc}$ -tetrofosmin. Lesions that concentrate ^{201}Tl appear to be more aggressive and are associated with higher Tg production. Despite better resolution of $^{99\text{m}}\text{Tc}$ labelled agents, all three radiopharmaceuticals have shown very similar sensitivity and specificity and should complement rather than replace ^{131}I . They offer the extra advantage of being performed while patients are on suppressive thyroxine therapy thus avoiding unpleasant symptoms of hypothyroidism. Whole-body ^{18}F FDG-PET is perhaps of higher sensitivity but its use remains restricted due to high cost and limited availability.

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16. LONG TERM FOLLOW-UP

Thyroid cancer patients survive for several years and hence it is essential to keep them under constant observation and surveillance in order to pick up abnormalities and institute appropriate treatment. The strategies that need to be developed will therefore depend on the expected changes that are likely to be observed in the patients resulting from (a) the long term effects of radioiodine therapy, medical management of thyroid cancer and post-surgical effects, and (b) the outcome of the disease process itself such as recurrences, distal metastases and mortality.

The behaviour or the outcome of the disease can be assessed by two important criteria, namely, (a) *recurrence* of the disease and (b) *survival* of the patient. These two outcomes need to be evaluated in detail in order to understand and/or predict the occurrence of either. The factors which determine the outcome may be related to the biological behaviour of the tumour, the reactions and physiology of the host and the treatment given to the patients, either alone or interrelated to each other.

Recurrence or reappearance of the disease either locally in the neck or at distant sites leads to an increased morbidity and a mortality varying between 40-50% [16.1, 16.2]. Recurrence as an event is reported to be an independent predictor for survival [16.3]. The prognosis of the recurrent disease depends upon the site of recurrence and whether or not the patient has experienced a disease free interval (DFI). A relatively better survival is predicted if the recurrence site is local or regional, while the mortality and morbidity is higher for recurrence at distal site. Recurrence of the disease has been defined as the appearance of a new site of growth after a DFI of a minimum period of one year (DFR) or if a new site appeared in an existing disease is called persistent disease. Recurrence was also defined as overall or total independent of the site or number of lesions, also denoted as '*any recurrence*'.

16.1. Recurrence of papillary thyroid cancer

The reported wide variation could be due to the effect of a number of factors related to the population examined, ethnic and geographical influences, the varied and wide ranging opinions and methods of treatment for primary Papillary thyroid cancer and the extent of rigor and vigilance employed for a long term follow-up.

The probability of the disease to recur in RMC patients with papillary cancers at 10, 20 and 30 years was 11.5%, 18.3% and 18.3%, respectively (Fig. 16.1), with a mean time of 4.2 years (median, 3.0 years; range, 1 to 28 years). A majority (94.1%) of recurrences occurred within the first 10 years. In this experience there was only one late recurrence at 28 years. The reported probability for overall '*recurrence*' to occur has been 15% at 5 years, 26% at 10 years, 27% at 15 years and 31% at 30 years [16.4]. In some studies the recurrence of disease has been reported to occur even after 2 to 3 decades [16.5-16.9]. The observed lower recurrence rate as well as the absence of the late onset of recurrences after the first decade in this series is probably due to treatment strategy of total thyroidectomy (TTx) and adjuvant, along with thyroid hormone medication.

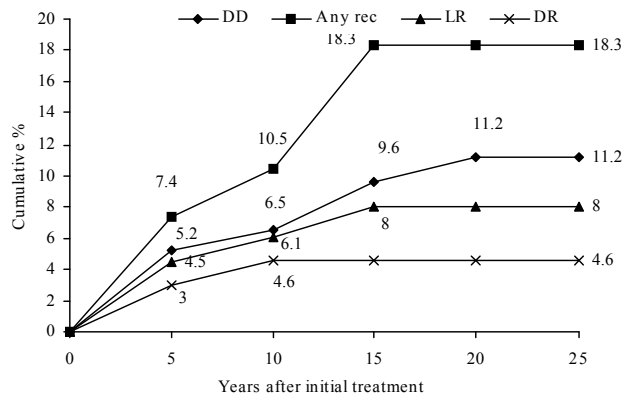


FIG. 16.1. K.M. curves for survival, any, local and distal recurrences in papillary cancer patients.

Among other factors that may influence the incidence and the time of onset of recurrence are: (a) the ‘extent of disease’ at initial presentation, (b) age at diagnosis, (c) type of recurrence, (d) site to recur and (e) the ability to concentrate ¹³¹I. The ‘extent of the disease’ influenced the ‘recurrence’ rate at the end of 5 years being 5.6%, 11.2% and 16.2% in intra-thyroidal, regional and distal disease, respectively which was statistically significant ($p < 0.00001$). The time to recur was significantly longer in patients with intra-thyroidal disease as compared to those having nodal or distal disease at initial presentation. Contrary to the common belief, the DFR recurrences were higher (see Fig. 16.2) in those who had only intra-thyroidal disease at presentation followed by patients with nodal disease indicating that in the former group there is a chance of recurrence even when one may feel that the patient is cured. As high as 62% of the recurrences were non-iodine concentrating indicating that the biological features of recurrent disease is different from that of the original disease.

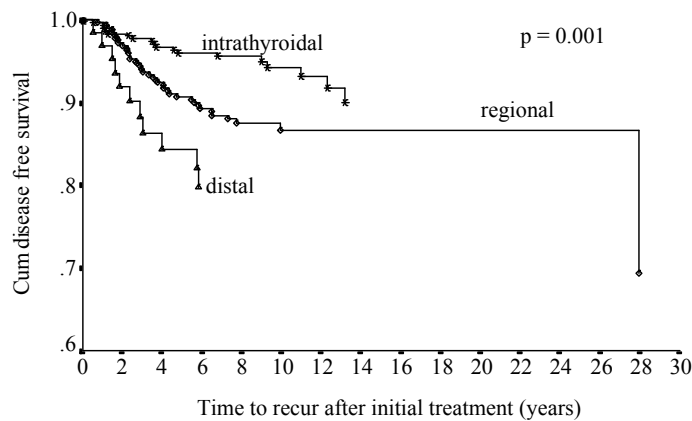


FIG. 16.2. Time at which recurrences occur in patients who presented with thyroid nodules, nodal and distal metastases.

Reported literature supports the higher tendency of PTC to recur to regional lymph nodes [16.7, 16.8]. The mortality due to local recurrence varies between 17-64% [16.9-16.13]. In a well designed study of 963 patients Grant and colleagues [16.9] reported that local recurrence in the remnant bed, was not fatal, however, in older patients with locally invasive disease it is associated with death. In this report, age greater than 60 years, extent of tumour, tumour size of 4 cm, type of surgery and time period of surgery were found to be significant predictors by

univariate analysis. In 535 patients of papillary microcarcinoma, Hay and associates [16.14] have observed that the LR were more likely to occur in node positive patients as indicated by multivariate analysis. In a larger series, in patients who had a potential curative operation at their initial treatment, these authors reported that an age less than 20 years, tumour size greater than 4 cm, presence of nodes and locally invasive disease were significant predictors for nodal recurrence by univariate analysis. The reported incidence of *Distal Recurrence* (DR) varies between 2.0-12.4%. The probability for the disease to recur at 30 year was 23%.

16.1.1. Multiple episodes of recurrence

It is not uncommon to have more than one recurrence in PTC. Disease recurred repeatedly in the same individuals, twice in 33.9%, thrice in 37.9% and four times in 31.8%. The most frequent sites were the nodes followed by the lung and bones. The brain was the most common site for secondary and tertiary metastatic recurrences. Similar findings of DM to brain as a frequent common site of late recurrence have been reported by Dineen, et al. [16.12] in an analysis of a 100 cases of DM in PTC. A life-long monitoring of patients is therefore mandatory.

16.1.2. Survival

An *overall mortality* rate of 6.6% observed in patients is within the reported range of 1.6-27% (Fig. 16.3). This was attributed to the rather low mortality observed in patients to the vigorous multimodal treatment offered. The K-M probability for survival was 94.8% at 5 years, 93.5% at 10 years, 90.4% at 15 years and 88.8% at 20 years after which no death was recorded till a 32 year period. The reported probability for survival has been 60-99% at 5 years, 50-97% at 10 years, 35-95% at 20 years and 78-93% at 30 years.

The mortality was related to the 'extent of disease' with 1.9%, 7.8% and 23.5% in intra-thyroidal, regional and distal disease.

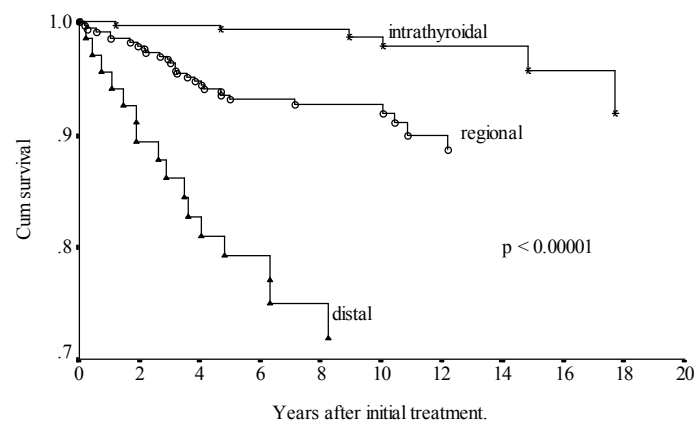


FIG. 16.3. Probability of survival of papillary cancers who present with thyroid nodules, nodal or distal metastases.

TABLE 16.1. MORTALITY AND EXTENT OF DISEASE AT INITIAL PRESENTATION

	Extent of disease			Total (n= 739)
	Intra-thyroidal (n= 323)	Distal (n= 68)	Regional (n= 348)	
<i>Death from cancer (%)</i>	6 (1.9)	16 (23.5)	27 (7.8)	49 (6.6)
<i>Death due to recurrence</i>	6	4	12	21
<i>Age at diagnosis (years)</i>				
mean	46.7	53.5	58.6	55.8
median	48.5	53.5	58	55
<i>Age at death (years)</i>				
mean	55.4	54.6	62	57
median	55	55	61	59
<i>^aTime to die (years)</i>				
mean	9.5	3.1	4.1	4.5
median	9.5	2.8	3.2	3.2

^a Time to die: local vs regional, p= 0.004; local vs distal, p= 0.002.

Some of the factors associated with recurrence and death are shown in Table 16.1. The presence of non-functioning metastases (NFM) had an adverse outcome for (a) (Fig. 16.4) 'recurrence' (b) (Fig. 16.5) DR and (c) mortality. Adverse outcome in patients with NFM has been observed by others [16.14-16.16].

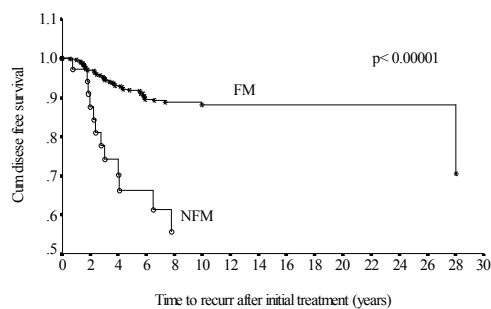


FIG. 16.4. Shows recurrence in NFM.

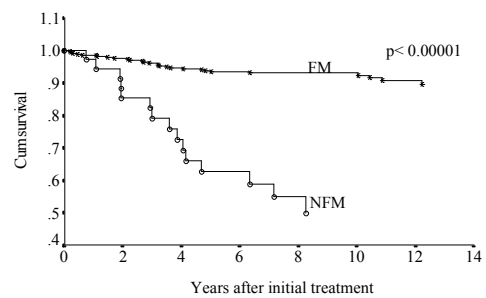


FIG. 16.5. Shows survival rate in NFM.

It has been argued that necrotic tumours lose the capacity to concentrate ^{131}I . However, as these tumours grow very rapidly, it is likely that they have become less differentiated resulting in reduced capacity for ^{131}I uptake. In this series, the 5 and 10 year survival rate in metastases concentrating ^{131}I was 93.8% and 93.1%, respectively, while the corresponding value for NFM was 58% and 49.8%, respectively. As observed by us and reported by others, the metastasis that concentrate ^{131}I i.e. Functioning Metastases (FM) have longer survival than those with NFM. The 10, 20 and 30 year survival rate in patients with nodal disease was

92.7%, 88.8% and 88.8%, respectively. The survival for patients in intra-thyroidal and nodal disease is believed to be excellent as evident by overall survival rates of 96-98% and recurrence rate of less than 10% [16.21]. Distant metastases portend poor prognosis regardless of treatment as observed by us and reported by others [16.22,16.23]. A better survival with lung disease has also been reported. Pulmonary metastases concentrating ^{131}I in young patients have a better outcome.

16.2. Recurrence of follicular cancers

The 'recurrence' rate was positively correlated with the extent of the disease, (7.1%, 20.0% and 26.0% in intra-thyroidal, regional and distal disease, respectively) indicating that the metastatic disease already present (in the cervical nodes or in distant regions) tends to recur more often as compared to that without metastasis (Fig. 16.6).

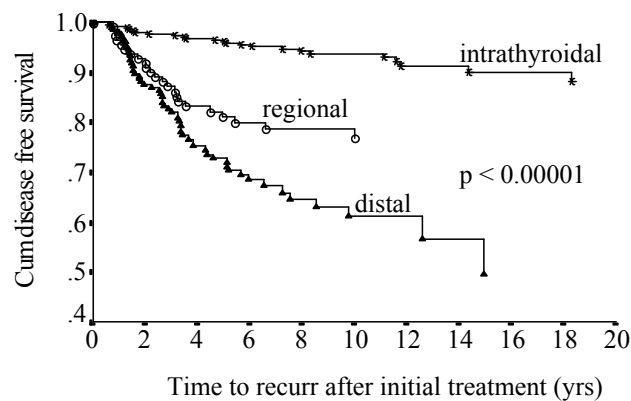


FIG. 16.6. Shows recurrence rate in follicular cancer when presented with thyroid nodule, nodal and distal metastases.

The mean time to recur in patients with intra-thyroidal disease was 5.9 years which was significantly longer than those which occurred in patients with metastatic regional (2.9 years) and distal disease (3.4 years) at initial presentation. Of the total 104 'recurrence', 34.6% were DFR suggesting that a higher percentage (65%) of recurrences occurred in an already existing disease. A larger proportion of recurrences were DFR in patients with intra-thyroidal disease (82.6%) as compared to 43.5% and 12% seen in those with regional and distal disease, respectively. In other words, patients with DM have a lesser chance to be cured and have progressive disease while those with intra-thyroidal disease tend to experience a longer disease-free interval. The predominant *sites of recurrence* were 36.5% in nodes, 21.2% in the skeletal system, 15.4% in the lungs and mediastinum, 15.4% in the multiple sites, 6.7% in the thyroid bed and 4.8% at other rare sites such as brain and liver.

The DR also significantly ($p < 0.00001$) differed with the extent of the disease (4.1%, 3.5% and 18.8% in intra-thyroidal, regional and distal disease, respectively) at initial presentation. These findings suggest that the regional disease at initial presentation tends to recur loco-regionally, distal disease tend to recur more distally, and intra-thyroidal disease could metastasize with equal frequency to the cervical nodes or to distant sites. The overall *mortality* in the recurrent disease was 54.8%. The death due to recurrence may vary between 0.0-100%. In fact in one study, it has been shown as an independent predictor for adverse outcome [16.26]. The rather high mortality resulting from recurrence of disease indicates that

treatment should aim at reducing the recurrence to a low level so that eventually the mortality due to cancer can be reduced and controlled.

16.2.1. Survival

An overall 30-year mortality rate of 21.0% (139/663) seen in this series is well within the published range of 3.3-64%. The average age at death was 52.3 years (median, 52 years) and average age at initial presentation was 43.3 years. The mean time for cancer specific death for 139 patients was 4.6 years (median 3.9). About 96.4% of the deaths occurred within 15 years indicating that death at a later period is rare. In a series of 49 patients, DeGroot, et al. [16.26] did not observe any death or recurrence after 13 years. In another study, no recurrence or death was recorded 10 years after treatment.

There was a direct relationship between mortality and extent of disease (3.1%, 15.7% and 49.8% in intra-thyroidal, nodal and distal disease at initial presentation, respectively). The mean time to die was significantly longer ($p= 0.003$) for intra-thyroidal disease (7.6 years) as compared to 4.2 years in distal disease at initial presentation. An improved survival rate in recent years has been reported by others also [16.27,16.28]. This has been perhaps because of early diagnosis and availability of sophisticated techniques for management of the disease. An individual with nodal disease is therefore at a high risk for mortality if the (a) nodal disease does not concentrate ^{131}I , (b) disease recurs and (c) ^{131}I treatment has not been received.

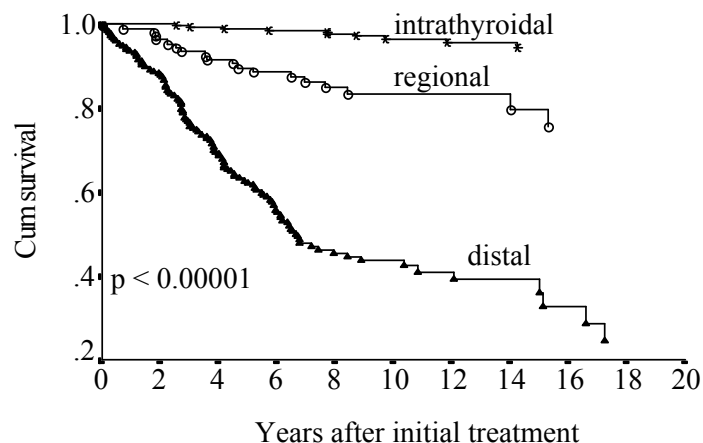


FIG. 16.7. Survival rate of follicular cancers when presenting with thyroid nodules, nodal or distal metastases.

The recurrence and the mortality rate were 26.0% and 49.8%, respectively for patients with distal metastases (Fig. 16.7). The presence of DM has a poor outcome and is the prime predictor both for mortality and recurrence in univariate analysis as observed by us, and reported by others. The 10 and 15 year survival for patients with pulmonary metastasis in this series was 74.8% and 68.6%, which is much higher than the corresponding values of 28.9% and 11.4% reported by Nemeč, et al. [16.31]. The outcome of the disease depends upon the site to recur, with a better outcome for pulmonary metastasis, which concentrate ^{131}I [16.13, 16.32] and are micronodular in nature [16.33]. In this study, the 5-year survival rate (63.5%) for patients with DM concentrating ^{131}I (FM) was higher than 43.8% seen with NFM. Similar findings of better survival in metastatic disease concentrating ^{131}I as compared to those, which do not concentrate, have been observed by others also [16.33, 16.34]. In a patient with DM,

the disease tends to recur regardless of host factors, tumour features or treatment modality. However, a patient with DM is at a 'high-risk' for mortality if he (a) is above 34 years and (b) has not received ^{131}I treatment. The reported factors in univariate analysis in 85 cases of DM have been age at diagnosis, extent of disease, lung pattern, ^{131}I uptake and treatment [16.35].

Follicular carcinoma is believed to have a more aggressive course of disease as compared to PTC, because it is a disease predominant in the elderly age group, where tumours are believed to be large, more invasive, less differentiated and have a propensity to metastasize to distal sites. When matched for age and sex, the mortality in follicular and papillary types of the tumour has been comparable. With a comparable stage of the disease and similar age the survival does not differ significantly between the PTC and FTC. The outcome of a minimally invasive FTC confined to the thyroid bed and intra-thyroidal PTC is reported to be excellent.

In one [16.36] series, the 6.3% mortality in FTC was not significantly different from 5.4% in PTC in patients without the presence of DM. When the age was matched decade wise for 663 patients of FTC and 739 patients for PTC, except for the extreme ages; below 19 years and above 60 years, there was a significantly higher death rate of 3.1%, 12.1%, 27.3% and 33.6% for age groups in 3rd, 4th, 5th and 6th decade in FTC as compared to 0.0%, 1.5%, 10.1% and 17.8% for the respective age groups in PTC. There was no significant difference in the mortality rate when the intra-thyroidal disease was matched for both types of histology. There was a significant difference ($p= 0.024$) in mortality rate between FTC (14.8%) as compared to PTC (7.8%) for nodal disease as well as distal disease ($p= 0.0002$). Nodal disease in FTC has a poorer prognosis than that in PTC. Distal metastases also had a poorer prognosis in FTC. This is because skeletal metastasis was a predominant site in FTC while incidence of the pulmonary metastasis is higher in PTC. The lung metastasis had a better prognosis as compared to skeletal metastases as observed by us and reported by others (Table 16.2). In contrast, some studies have reported comparable results between the two types of tumours when matched for the extent of the disease.

TABLE 16.2. COEFFICIENT AND HAZARD RATIO FOR MORTALITY

Factors	Coefficient	Hazard ratio
Age 35 years	1.08	0.34
+ Local invasion	0.25	0.77
+ Distant metastases	1.13	0.32
+ Less well-differentiated tumour	0.24	0.78
No radioiodine treatment	0.34	1.4

Hence the above data indicates that frequent follow-up of patients for clinical evaluation and investigations such as whole body scans with radioiodine, $^{99\text{m}}\text{Tc}$ MIBI or Tetrofosmin, or ^{201}Tl chloride or ^{18}F FDG if available should be considered. Wherever noniodine concentrating disease is suspected other investigations such as CT scans, MRI or ultrasound studies should be done to localize disease in the presence of high levels of serum Tg. Early detection is essential for instituting therapy with Radioiodine when concentration is observed or surgery where possible and external radiotherapy if disease is extensive and surgery is not possible or disease removal is partial.

The other strategy employed in the follow-up of patients is to look for the effects of the treatment given to the patient. Radioiodine therapy is known to produce chronic side effects and these have to be carefully assessed at the time of the follow-up.

16.3. Postsurgical side effects

One of the consequences following aggressive thyroid surgery is Hypoparathyroidism (HPT) leading to hypocalcemia. This could be transient or permanent in nature requiring frequent administration of calcium (Ca^{2+}) along with calciotropic substances. The calcemic status of the patient following thyroid surgery depends upon the degree and the extent of damage or loss of the parathyroid glands. The incidence of post operative HPT inducing hypocalcemia is reported to vary from 3-32% as shown in some of the series (Table 16.3), depending upon whether the type of surgery is a total or partial thyroidectomy [16.59-16.61].

TABLE 16.3. REPORTED INCIDENCE OF HYPOPARATHYROIDISM CONSEQUENT TO THYROIDECTOMY

Author	No. of patients	Type of thyroidectomy	Years followed	Per cent hypoparathyroidism
DeGroot, et al. [16.5]	177	Total	12	8.4
	32	Lobectomy	12	2.5
McConahey, et al. [16.20]	136	Total	39	22
	163	Lobectomy	39	4.3
Farrar, et al. [16.60]	29	Total	10	20
	126	Lobectomy	10	1.6
Cohn, et al. [16.59]	53	Total	15	21
	37	Lobectomy	15	2.7
Hay, et al. [16.6]	138	Total	-	32
	721	Lobectomy	-	0.3

A retrospective analysis of calcemic status of 500 randomly selected patients, who underwent Total Thyroidectomy (TTx) for Differentiated Thyroid Carcinoma (DTC) was studied. These patients were followed up from a minimum of 2-3 years, to a maximum of 15-20 years, and calcemic status was ascertained at varying times following their surgery and radioiodine (^{131}I) therapy. The minimum period of ascertaining Ca^{2+} status varied from 4-6 weeks after surgery, to at times several years later.

The over all distribution of these patients in different age groups in both the sex, indicated the predominance of female population (Fig. 16.9). All these patients were normo-calcemic prior to their thyroid surgery. They were investigated for the circulating levels of Ca^{2+} before ^{131}I treatment and further on every follow-up examination and evaluation.

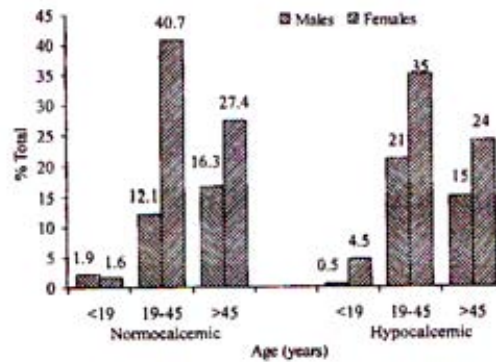


FIG. 16.8. Calcemic status and gender of the patients after thyroidectomy.

The objectives of the therapy are to restore the serum Ca^{2+} concentration high enough to prevent complications of hypocalcemia but not high enough to lead to hypercalcemia. In general the serum Ca^{2+} should be kept at or below the lower end of normal to prevent hypercalcemia (Fig. 16.8). The post surgical HPT may require higher doses of vitamin D or its more active metabolites for effective management of hypocalcemia. Regular monitoring, preferably at 3-6 months intervals is necessary to detect any spontaneous changes which some times occur, besides controlling the patient at a satisfactory level of serum Ca^{2+} [16.62]. Calcium supplements are generally used, and it is essential that a regular diet must be fortified with at least 1 g/day of elemental calcium, preferably in 2-3 divided doses on an empty stomach to facilitate its increased absorption. One gram of calcium is present in 2.5 g of calcium carbonate, 5 g of calcium citrate, 10 g of calcium gluconate, 8 g of calcium lactate and approximately 3.5 g of calcium hydrogen phosphate.

There are now a wide variety of choices for treatment with vitamin D and/or its more active derivatives. Vitamin D in the dose range of approximately 25 000-100 000 I.U. along with calcium-supplementation has the longest duration of action and can result in prolonged toxicity, if left unmonitored. Recently there has been widespread use of more active metabolites of vitamin D which include Calcidiol (25 hydroxy vitamin D, 25-200 $\mu\text{g}/\text{day}$) and Calcitriol (1,25 dihydroxy vitamin D, 0.25-1 $\mu\text{g}/\text{day}$). These help in the increased mobilization of Ca^{2+} from intestine and bone, particularly Calcitriol.

The decision to treat hypocalcemic patients, further rests upon both the degree of hypocalcemia and the rate at which the condition develops. Mild to moderate hypocalcemia (~ 8.0 - 8.5 mg/dl) that is asymptomatic in many cases, warrants, cautious observation. Though medical emergencies due to severe hypocalcemia are rare [16.63-16.64], serum Ca^{2+} levels of <7.5 mg/dl or patients with hypocalcemic symptoms, must be treated promptly and further need to be monitored regularly, as the diagnosis of chronic/severe hypocalcemia is often missed. This is because the patients may present with bizarre complications viz. seizures, papilloedema, cataract, ectopic calcification of basal ganglia or psychiatric problems. An illustrative case report of a patient in this regard by Gupta [16.64] in his series of hypocalcemia, is worth noting.

16.4. Long term complications of radioiodine treatment

16.4.1. Chronic sialadenitis

A significant number of patients treated with ^{131}I for carcinoma of thyroid often complain of symptoms like dryness of the mouth, pain in the parotid region, altered taste, and difficulty in

swallowing, poor oral hygiene and loss of appetite. Information regarding the effect of ^{131}I on salivary glands, and the extent of damage produced is scanty.

Salivary gland function can easily be measured by radioisotope scintigraphy. Quantitative parameters of salivary function using pertechnetate have been reported. Malpani, et al. standardized a simple protocol for assessing salivary gland function using $^{99\text{m}}\text{TcO}_4^-$ (pertechnetate), a) so as to study the effect of varying dosages of ^{131}I given for ablation of residual thyroid or metastases on the salivary glands, b) to try and explain the symptoms in the treated patients and at the same time, c) document the incidence and duration of salivary dysfunction [16.36]. The per cent uptake and excretion of $^{99\text{m}}\text{TcO}_4^-$ by the salivary glands in controls (only thyroidectomized) and the ^{131}I treated patients is shown in Table 16.4. There was a significant ($p < 0.05$) reduction of uptake in the ^{131}I treated group as compared to controls. Similarly, the per cent excretion of $^{99\text{m}}\text{TcO}_4^-$ by the salivary glands after sialogogue stimulation was significantly reduced ($p < 0.05$) in patients as compared encountered in this serial study may be negligible.

TABLE 16.4. SALIVARY GLAND UPTAKE AND EXCRETION OF $^{99\text{m}}\text{TcO}_4^-$: EFFECT OF ^{131}I TREATMENT

	Salivary gland complex					
	% Uptake (mean \pm SD)			% Excretion after sialogogue stimulation (mean \pm SD)		
	Left	Right	Both	Left	Right	Both
A. Thyroidectomized controls (n= 14)	0.73 \pm 0.15	0.70 \pm 0.14	1.43 \pm 0.27	49.71 \pm 10.28	49.6 \pm 11.0	49.82 \pm 10.0
B. treated Symptomatic (n= 12)	0.61 \pm 0.40	0.55 \pm 0.27	1.16 \pm 0.66	29.74 \pm 21.86	31.86 \pm 17.6	31.39 \pm 18.14
C. treated Asymptomatic (n= 21)	0.59 \pm 0.30	0.62 \pm 0.32	1.21 \pm 0.57	36.35 \pm 24.42	39.46 \pm 24.98	38.38 \pm 23.65
D. treated Total (n= 33)	0.60 \pm 0.33	0.59 \pm 0.30	1.19 \pm 0.59	33.95 \pm 23.04	36.7 \pm 22.59	34.20 \pm 21.86

Note: The data referred to above (i.e. % uptake and excretion of both salivary glands combined) was tested for statistical significance by Mann-Whitney test (two-tailed test between various groups) and the respective 'p' values were as follows: — for uptakes: A vs D; $p < 0.05$, A vs B; $p < 0.05$, A vs C; ns, B vs C; ns, — for excretion: A vs D; $p < 0.05$, A vs B; $p < 0.01$, A vs C; ns, B vs C; ns.

Reports indicate that chronic sialadenitis with xerostomia can occur in 12% of subjects. Reserpine has been used to protect glands, however, the benefits are doubtful [16.37]. Transient salivary gland pain can be treated with anti-inflammatory drugs. An increase of salivary gland tumours has been reported. In this series no such case has occurred.

16.4.2. Radiation effects on gonads and fertility

One of the most dreaded and over exaggerated effects of ^{131}I therapy has been the effect on the gonads. This is mainly because of the long term survival and the involvement of young individuals. The radiation dose estimated to be delivered to the testes according to MIRD

methodology is 3.108 cGy/MBq (0.084 cGy/mCi) of therapy dosage. A review of the gonadal radiation effects on human and animal studies estimated the LD50 for human spermatogonia at 15-33 cGy.

16.4.2.1. Male gonadal function

Since there is a possibility of radiation effects on the gonads with ^{131}I therapy, Follicle Stimulating Hormone (FSH) and testosterone levels were studied in 103 males for 93.7 ± 54 months [16.38]. The ^{131}I dosages given ranged from 30-1335 mCi (1.11-49.4 GBq). The mean FSH values were found to be higher in treated males than in controls and a positive correlation between FSH and the cumulative ^{131}I dosage was observed. Sperm analysis revealed minor changes in sperm mortality. Occasional documentation of permanent azoospermia is reported. However, reports of infertility are rare, despite the transient impairment of testicular germinal cell dysfunction [16.39]. Long term follow-up of young males treated below the age of 21 years and followed for 19 years revealed 12% incidence of infertility which was not significantly different from that of the general population.

In this study of 15 males younger than 21 years, treated with ^{131}I dosages varying from 100-500 mCi (3.7-18.5 GBq), only 1 case of azoospermia was recorded. No infertility was present in the others who had married over the years. Short-term infertility which lasted for 22-26 months has been documented [16.37]. The radiation effects are hence dosage dependent and in most cases reversible. To reduce gonadal irradiation it is advised that the patient should drink plenty of water and void frequently for the first 72 hours after ^{131}I administration. Another study on the long term effect of ^{131}I on male fertility in children and those given large dosages of ^{131}I reported a normal fertility.

16.4.2.2. Ovarian function and fertility

Female gonadal function and fertility has been documented in a few reports [16.39]. Ten to thirteen per cent of female children treated with ^{131}I had a transient infertility for 3 and 14 years followed by a normal successful pregnancy. A more recent study from Italy showed no significant difference in the fertility rate and prematurity in a large series of 627 women treated with ^{131}I [16.40]. Over the years data has been published on a large series of women treated with ^{131}I with no demonstrable effects on fertility or on the incidence of congenital abnormalities in children borne by these women (Table 16.5).

In this series it was seen that 66 subjects (51 females, 15 males) treated with ^{131}I had later married and had children. The age of the parents at the time of treatment varied between 15-35 years. Children were born between 1.2 to 23 years after treatment with an average time period of 6 years after therapy. Of the 91 children born, 68 were normal, 4 children died due to infectious diseases while no information was available in 5 children. There was 1 abortion and 1 premature birth. The status in 17 was unknown. No congenital abnormalities were reported. A comparison with data published so far indicates that there is no significant effect of ^{131}I on the children born to parents treated with ^{131}I therapy especially if an interval of 2 to 3 years has elapsed after treatment.

Transient short-term ovarian failure has been reported in 25% women with amenorrhoea and the FSH rose for the first year after therapy [16.41]. In general the gonadal fear has been overstated and observation of thousands of patients treated all over the world reported no significant effects (Table 16.5).

TABLE 16.5. OUTCOME OF PREGNANCY IN WOMEN TREATED WITH ¹³¹I

References	Dose of (mCi)	Age at conception	No. of pregnancies	Infertility (%)	Miscarriages or abortions (%)	Still births (%)	Live births		Death <1 a (%)	Gonadal doses (cGy/GBq)	Malformations (%)
							<Term	Low birth wt			
Schlumberger, et al. [16.48]	0-100	<35 yrs	1252	-	11	2	5	10	1	10.8	3
		>35 yrs	261	-	2.5	3	8	10	3		
Casara, et al. [16.13]	118-680	<36 yrs	73	-	2.8	0	0	4	0	5.46	1.3
Dottorini, et al. [16.40]	50-1500	-	65	0	1.5	4.5	3	0	0	5.4	1.5

16.4.3. Pregnancy after high therapeutic dosages of ¹³¹I

Opinions and recommendations regarding pregnancy after ¹³¹I ablation of residual thyroid tissue or treatment of metastatic disease is discordant. Radiation exposure is known to represent a risk to the foetus. Chromosomal aberrations are known to occur at a higher frequency after ¹³¹I treatment in peripheral lymphocytes of treated patients as compared to controls [16.42]. There are only a few reports on pregnancy and foetal risks in patients treated with ¹³¹I [16.43]. In one series only one case of severe cardiac malformation among 73 new born children was observed. In this mother the calculated gonadal dose was not higher than in other mothers [16.40].

In this report there were three children born with low birth weight. No association between Fallot's tetralogy and low birth weight with maternal gonadal radiation exposure was observed. It was presumed that high suppressive doses of thyroxin may have been an important factor in the low birth weight of neonates [16.44, 16.45]. The mild exogenous hyperthyroidism was probably responsible for the two spontaneous abortions which were recorded in this series. It was advocated that care should be taken to administer the lowest thyroxin dose capable of maintaining TSH suppression. On the basis of the data it appears irrational to dissuade young females treated with ¹³¹I from considering pregnancy. However, pregnancy should be delayed for one to three years after the last ¹³¹I administration. Whether the effect is due to gonadal irradiation or to insufficient control of hormonal thyroid status needs to be established. Overall the problems faced are not due to ¹³¹I but to the hormonal therapy which needs more stringent monitoring [16.46-16.48].

16.4.4. Malignant neoplasm

Induction of other malignant neoplasia and bone marrow damage are potentially more serious consequences. Two commonly reported manifestations are leukaemia and bladder cancer [16.39]. Incidence of bladder cancer has been reported slightly higher in these patients than seen in the general population [16.39]. Sporadic cases of other malignancies like carcinoma of the breast, melanomas and others are also reported. The cancer patients are probably an increased risk of developing the second malignancies compared to general population rather than a consequence of ¹³¹I therapy. The long survival time of patients would predispose them to development of another malignancy which occurs with the same frequency as those in an untreated population.

In this series, there were 39 cases of second malignancies. They were mostly females (62%) as compared to males (38%). Seventy two per cent of the patients were younger than 60 years. Thirty one per cent presented with second concurrent malignancies at the time of treatment, while 41% developed a second malignancy after 5 or more years. More than 88% of these patients had received less than 18500MBq (500 mCi) ^{131}I therapy. External radiation treatment was given to more than half of them primarily as a mode of therapy for the second malignancy.

Leukaemia associated with radiation has been well documented. With ^{131}I use, reports of leukaemia induction are recorded [16.49]. The risk indicates a low incidence in reported studies and is generally correlated with the total dosage of ^{131}I used especially when the ^{131}I activity in the blood exceeds 2960MBq (80 mCi) or more. Therefore, limits were set that single dosages should be less than 7400MBq (200 mCi) and cumulative dosages less than 29600MBq (800 mCi) per patient. These precautions would reduce the incidence of leukaemia to zero. A study has been reported on 46 988 patients, of which 36 326 were exposed to ^{131}I for diagnosis, 9860 for hyperthyroidism therapy and 802 for treatment of TC. When cumulative dosages were less than 29600MBq (800 mCi) and individual dosages administered were between 3700-7400MBq (100-200 mCi), the risk of incidence of leukaemia was found to be low. However, with cumulative dosages exceeding 37 GBq (1 Ci) the incidence of leukaemia may increase [16.53]. In this series only one patient died from chronic myeloid leukaemia (CML). This patient had CML before the onset of TC.

In one review of 13 large series of 2753 patients treated with ^{131}I the incidence of leukaemia was 0.5%. It was suggested that an incidence of 5 per 1000 cases is more than expected in the general population. Myelogenous leukaemia which occurs after ^{131}I therapy occurs within 10 years of exposure. The chances of developing leukaemia are lower if the interval between ^{131}I therapies is 12 months rather than a few months and if total doses are below 200 cGy to the blood. After constructing a careful decision matrix the conclusion was that the lifetime risk of leukaemia is so small (<0.33%) that it does not outweigh the benefit of treatment with ^{131}I .

16.4.5. Transformation to anaplastic carcinoma

The controversy regarding anaplastic transformation of DTC is not yet resolved. Whether anaplasia sets in as a course of the natural history of the disease or following ^{131}I therapy is purely conjectural. Some suggest that the repeated cycles of ^{131}I imaging, elevated TSH levels induced by hypothyroidism may be a contributing factor, others believe that ^{131}I destroys the functioning population of cells leaving the undifferentiated to survive and ultimately manifest in a anaplastic carcinoma as a terminal event.

16.4.6. Bone marrow suppression

Temporary marrow suppression is observed in patients treated with large dosages of ^{131}I . When 7400MBq (200 mCi) are administered about 35% cases show reduced haemoglobin levels, 10% reduced white cell counts and 3% platelet count reduction. This suppression is maximal at 4 to 6 weeks after therapy. Occasionally the white cell counts remain low up to 1 year. When the mean blood radiation dose exceeds 267 rads (45-740 rads) about 20% patients had serious bone marrow suppression [16.7]. However, studies at Memorial Hospital have not reported any temporary or permanent marrow suppression following the use of 75 mCi (2.78 GBq) ^{131}I dosages.

16.4.7. Effect of radioiodine therapy on renal system

Radioiodine is excreted mainly through urine. This results in significant radiation exposure to the kidneys and bladder during therapy. To determine whether the radiation dose delivered to the kidneys during ^{131}I treatment caused any renal impairment, urinary albumin was used as an index. Microalbuminuria indicates slightly elevated urinary albumin excretion and is a marker for glomerular damage. Tubular dysfunction with impaired protein reabsorption may also play a minor role in the excretion of elevated urinary albumin. Hence, an elevation in urinary albumin excretion after ^{131}I treatment will predict radiation-induced renal damage if it occurred during therapy. An in-house radio-immunoassay (RIA) has been standardized for the detection of microalbuminuria and used to estimate urinary albumin levels in patients treated with ^{131}I .

Figure 16.9 shows the urinary albumin concentration of the patients grouped on the basis of the total ^{131}I dosage received. Seventy-three patients were treated once, the remainder being treated two to six times. The median urinary albumin levels in these patients ranged from 2.4 to 12.9 mg/l.

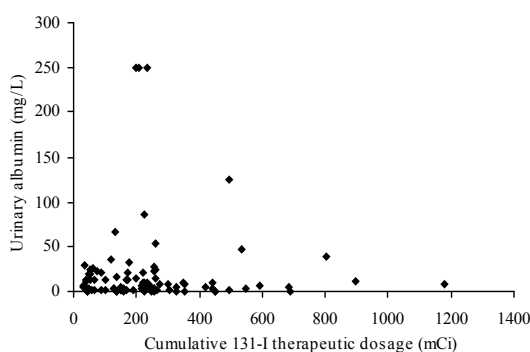


FIG. 16.9. Scatter diagram relating the urinary albumin concentration and cumulative activity of ^{131}I administered.

External X ray therapy given to patients with abdominal cancer can cause renal damage if the kidneys are included in the therapeutic field. They also stated that such therapy may lead to the development of acute or chronic radiation nephritis which causes proteinuria. Other complications of this therapy include benign or malignant hypertension and interstitial fibrosis. The renal tolerance dose for the external radiation therapy was 2300 cGy over 5 weeks and a dose of 2800 cGy or more delivered to both kidneys in 5 weeks or less would lead to renal failure.

The radiation dose delivered to the kidneys is 10 cGy for 1 mCi (37 MBq) of ^{131}I administered orally. The patient's kidneys are expected to receive 300-2500 cGy after the oral administration of 30-268 mCi (1.11-9.9 GBq) of ^{131}I . This is true in the case of intact thyroid gland, but where the thyroid tissue is not intact, the renal dose will be higher. No radiation dose measurements were performed in the present study. However, the incidence of microalbuminuria was not suggestive of renal damage after treatment with 30-268 mCi (1.11-9.9 GBq) of ^{131}I . There were no early or late effects of radiation on the kidneys. The radiation dose delivered to the kidneys following ^{131}I treatment of TC patients was within safe limits.

16.4.8. Radiation pneumonitis and pulmonary fibrosis

Patients with extensive diffuse pulmonary metastases that concentrate a high percentage of administered ^{131}I may develop fatal radiation pneumonitis or pulmonary fibrosis. Radiation pneumonitis was reported in 8.5% of the patients given ^{131}I treatment for metastases. To avoid this complication, the treatment dosage administered is such that no more than 80 mCi (2.96 GBq) of ^{131}I is retained in the whole body at 48 hours in the presence of pulmonary metastases.

The effect of large dosages of ^{131}I on the pulmonary alveolar-capillary membrane integrity as an index of pulmonary damage in 35 patients of thyroid carcinoma with pulmonary metastases was studied. Only one patient showed radiation induced damage to the lungs as measured by $^{99\text{m}}\text{Tc}$ -DTPA half-time clearance, pulmonary function test and chest X ray. Although the cumulative amount of ^{131}I varied from 158-1194 mCi (5.8-44.2 GBq) there were no demonstrable changes, which indicates that the incidence of radiation pneumonitis as a result of therapy is negligible and treatment with varying dosages is safe and without sequelae [16.53].

16.5. Problems of overdosage of thyroxine

Serum TSH has to be maintained at just below normal levels so as to maintain a suppressive state as TSH is known to stimulate the growth of thyroid remnants and cancerous cells. Generally the dose of Thyroxine required maintaining normal levels of serum TSH is in the range of 1.8 mg/kg of lean body weight. The dose of thyroid hormones in the elderly can be reduced by 20%. However, it is best to individualize doses to maintain the serum TSH levels to just below the normal values (between 0.1-0.5 $\mu\text{IU/ml}$). Elderly patients need to be monitored more closely as the symptoms of thyrotoxicosis are vague and often missed.

Two major side effects of overdose of thyroid hormones is reduction of bone mineral density and thyrotoxicosis. A recent review [16.54] on T4 therapy has raised a suspicion of the possibility of bone mineral loss especially in postmenopausal women. Several studies measured [16.55, 16.56] bone mineral density at different sites of the skeleton, including the femoral neck, vertebral bodies, and the calcaneum and it was concluded that postmenopausal women were at a higher risk of bone loss than premenopausal women. In both groups the risk was higher in those taking thyroid hormones. Similar studies have been reported in elderly men. These studies were conducted in post and premenopausal women on T4. The observation was a significant loss of bone calcium in those on T4 and this was more evident in postmenopausal women. Hence these high risk group patients need careful monitoring for adequate T4 replacement and study of bone density at regular intervals [16.57]. Necessary calcium supplementation should be included in the therapy.

Biochemical and physiological evidence [16.58] of elevated T4, high free thyroxine index and shortened systolic time intervals in clinically euthyroid individuals given standard doses of thyroid hormones. Hence extra care and evaluation of cardiac status is needed in elderly patients.

16.6. Diagnosis and management of residual, recurrent and metastatic MTC

The first indication of recurrent and/or persistent disease is a raised/rising serum calcitonin (CT) level. In the majority of cases, disease is usually localized to the neck/upper mediastinum. Computerized axial tomography is useful in identifying the disease. However, interpretation of images can pose difficulties due to distortion of anatomy after surgery.

Invasive disease is often occult and smaller than the threshold size detected by CT scans [16.65]. In such situations, better imaging agents are needed.

Radio-nuclide scanning with ^{131}I is not useful as MTC does not concentrate ^{131}I . On the other hand, scanning with $^{99\text{m}}\text{Tc}$ pentavalent dimercaptosuccinic acid $^{99\text{m}}\text{Tc}(\text{V})\text{-DMSA}$ has been reported to successfully localize in primary as well as recurrent and metastatic lesions with 50-80% sensitivity for detection of the disease [16.66, 16.67]. A positive scan in a patient with primary and cervical nodal lesions with $^{99\text{m}}\text{Tc}(\text{V})\text{-DMSA}$ is shown in Figure 16.10. The presence of skeletal metastasis can also be demonstrated using this compound. The sensitivity of detection of the primary and metastatic lesions in the nodes, lungs and bones, was about 75% in this series. The correlation of the results obtained with $^{99\text{m}}\text{Tc}(\text{V})\text{-DMSA}$ scans and serum CT level showed a specificity of 100% and sensitivity of 84%.

^{131}I metaiodobenzyl guanidine (^{131}I MIBG) which is used for the detection of neural crest tumours is reported to localize in 25-30% of MTC cases [16.68]. It was shown that $^{99\text{m}}\text{Tc}(\text{V})\text{-DMSA}$ is superior to ^{131}I MIBG and is an ideal agent in the follow-up of MTC patients (118). Accumulation of ^{201}Tl chloride in the primary and/or recurrent tumours is useful with a sensitivity of 95%, especially when the CT levels are elevated and conventional methods are negative.

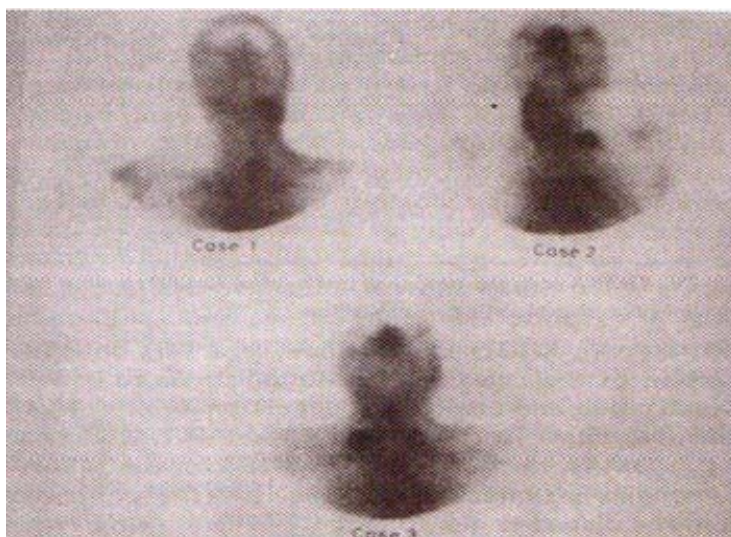


FIG. 16.10. The scintigraphic images showing the localization of radiopharmaceuticals in primary and metastatic sites. The pictures represent images taken 4 hours after (i.v.) administration of $^{99\text{m}}\text{Tc}(\text{V})\text{-DMSA}$ in patients of medullary thyroid carcinoma.

$^{99\text{m}}\text{Tc}$ -Methoxybutylisonitrile ($^{99\text{m}}\text{Tc}$ -MIBI) is described as a very interesting and useful compound in detection of metastasis and is found to score over ^{201}Tl chloride as it allows better visualization and anatomical details of lesions [16.70, 16.71]. A comparison of the utility of three agents ^{201}Tl , $^{99\text{m}}\text{Tc}$ -MIBI, $^{99\text{m}}\text{Tc}(\text{V})\text{-DMSA}$ (Fig. 16.10) clearly revealed the superiority $^{99\text{m}}\text{Tc}(\text{V})\text{-DMSA}$ to ^{201}Tl and $^{99\text{m}}\text{Tc}$ -MIBI for the follow-up of MTC patients [16.69]. DMSA studies are valuable, particularly, in the interpretation of CT scans when the anatomy is distorted due to surgery. The varying reported sensitivities of detection of the metastatic tumours could be due to the different mechanisms underlying the accumulation of various compounds. Blood flow, viability, tumour type, the sodium-potassium ATP-ase, the

cotransport system, the calcium channel system, vascular immaturity due to leakage and increased permeability have been described as possible factors responsible for the differences [16.72, 16.73].

The usefulness of pre-targeted immunoscintigraphy in the diagnosis and follow-up of patients with MTC has been reported recently [16.74, 16.75]. The antibody, either anti-CEA, anti-Chromogranin, biotinylated monoclonal antibodies either singly or both were injected, followed 24 hours later by avidin and another 24 hours later by ¹¹¹In labelled biotin. The sensitivity of 96% for detection of lesions with almost 100% specificity was reported in a series of 25 patients with MTC in one study [16.74]. In another study, the sensitivity of detection of known tumour sites was 90% and of occult disease in abnormal CT blood levels was 61% [16.75].

Metabolic imaging with positron emission tomography has been another important landmark in the detection of neoplastic tissues [16.76, 16.77]. Measurement of glucose metabolism in malignant tumours by means of ¹⁸F-fluoro-deoxyglucose has shown a good correlation between glycolysis and malignancy.

16.6.1. Persistent or recurrent hypercalcitoninemia

It is not uncommon to find persistent elevation of the serum CT level in patients of MTC, following primary surgery with no evidence of the presence of disease, either clinically, radiologically or special radionuclide scanning [16.70, 16.71]. In practice, persistent hypercalcitoninemia was observed in 24% of patients with no detectable lesion(s). These patients have been under observation for an average of 3-5 years and appear to be free of observable disease. The presence of microscopic metastasis may explain the raised levels of CT and the negative images. Another explanation could be the secretion of CT by ectopic neoplasia [16.78]. In a study of patients who presented with palpable tumours, 15 of 18 (83%) with hereditary disease and 11 of 20 (55%) with sporadic tumours had persistently elevated CT levels post-operatively.

Controversy exists as to the management of these patients. The majority of surgeons practice the wait and watch policy, provided the basic procedure of a total thyroidectomy with a meticulous central compartment clearance has been performed. This philosophy is based on the fact, that in the majority of these patients, it is impossible to localize the site of metastases either clinically or by imaging. Moreover, these biochemical recurrences are usually indolent and remain confined to the neck or upper mediastinum for prolonged periods of time. Delayed surgery, when the disease is manifested has not been shown in the literature to have a detrimental effect on survival. In a study of 18 patients, 16 had persistently elevated CT following 'adequate surgery', Block, et al. [16. 79] found that CT levels remained stable for up to 6 years and advocated observation in the absence of clinically manifest disease.

Reports on patients who have undergone re-operation for persistent hypercalcitoninaemia due to demonstrable disease and who had a variety of surgical procedures performed show that CT values rarely normalize, decrease less frequently and continued to remain high in most of the cases [16.80]. However, these patients do well. Even in patients who had a SVC for localizing the site of elevated CT levels followed by re-operation with directed node dissection, CT values does not normalize. Till a definite consensus is reached as to the correct management of these patients a strict surgical discipline is called for at the time of initial surgery for MTC. This would result in more biochemical cures and minimize the number of repeat neck surgery.

16.6.2. Recurrence

The incidence of local and distant metastases is high even at the time of initial presentation of the patient. In this series the recurrence rate was 53.5%. The site to recur was predominantly in the cervical nodes (68%) followed by skeletal (11%) and lung (4.5%). Seventy two per cent of these recurrences occurred on a single occasion while 24.6% occurred on two occasions and 3.3% occurred on three occasions. This suggests that recurrences can occur several times even after treatment is given for the first recurrence. The mean time for recurrence to appear was 4.6 years (median, 2.0 years). Nodal disease was surgically removed by a radical neck dissection. Medullary thyroid carcinoma is often an indolent disease that remains in the neck for long periods of time. Thus, the removal of recurrent disease may arrest the course of the disease.

16.6.3. Survival

The survival rate varies between 69-81% at 5 years [16.81], 48-71% at 10 years [16.81], 48-53.7% at 15 years [16.82] and 30-33% at 20 years [16.83]. The 5 and 10 year survival for sporadic and familial type combined has been 87.8% and 77.1%, respectively for females and 68.9% and 46%, respectively for men [16.81]. The 10-year disease free survival (recurrence free) has been 53% [16.84]. The locoregional recurrence free survival (Fig. 16.11) for 5 years has been 54% and for 10 years 42% [16.83]. The 5-year disease free survival is less than 35% in patients with MEN IIb.

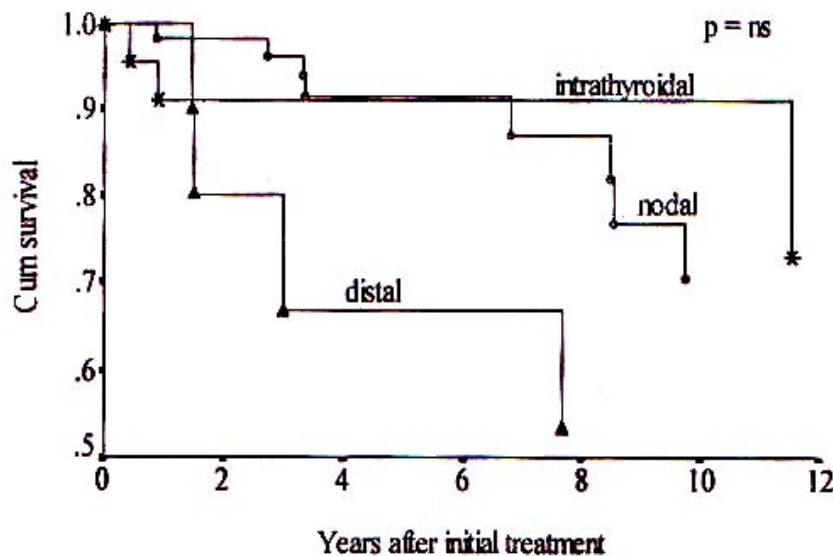


FIG. 16.11. The K-M type probability of survival with respect to intrathyroidal, regional and distal disease.

16.6.4. Summary

Medullary thyroid carcinoma is a biologically distinct form of thyroid cancer and accounts for 5-10% of all thyroid neoplasms. Twenty per cent of MTC can occur in a familial setting either by itself or as part of the multiple endocrine neoplasm syndromes. A disciplined approach is necessary in the work-up of these patients to rule out coexistent endocrine tumours (pheochromocytomas and parathyroid).

Calcitonin is a sensitive tumour marker secreted by MTC that is of prognostic value and important in the follow-up of patients. Surgery is the mainstay of treatment with a total thyroidectomy and central compartment clearance being the minimum for patients without cervical adenopathy. Radiotherapy has a limited role and is only indicated as a palliative measure in patients with advanced/metastatic disease not amenable to surgery. Meticulous surgery is essential to ensure a return of serum calcitonin levels to normal. The approach to patients with persistent hypercalcitonemia without manifestation of disease is still not clear, with the literature divided between a wait and watch policy as against aggressive surgical application.

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17. REGIONAL EXPERIENCES

17.1. Introduction

In the quest for the optimal management regimen for patients with thyroid cancer, as with health-care in general, the trend in much of the world is, where possible, to practice 'evidence-based medicine'. The Cochrane Collaboration has established a data-base and data classification system in order to facilitate this approach [17.1]. As will become apparent from this section, when consideration is given to all countries of the world, many factors limit such an idealized approach. Furthermore, randomized control trial data, which is the highest ranked of the Cochrane Collaboration data type, is not available for many diseases, and in many cases is not appropriate.

Conformity and diversity of medical practice can each be regarded as a double-edged sword. Conformity sets standards and allows monitoring of quality assurance and regulation but limits the utility of medical practice to those with the resources required for its implementation. Diversity facilitates knowledge by experience gained under a range of conditions but in some cases may result in lower standards of medical practice. In order to improve global standards of health care, it is important to understand the reasons for diversity of medical practice and to regard such diversity as an evolution toward the best possible practice rather than applying the label of inferior or sub-standard medical practice. Analysis of the world literature by computer search can indicate the relative research activity levels in countries around the world. For example, searching cancer literature through CANCERLIT, using the key word 'thyroid', there are 107 citations that directly relate to thyroid cancer for the year 2001. These come from 23 different countries but the majority come from the USA (34%), Italy (16%), Germany (11%) and Japan (9%). On a continental basis, the ranking is Europe (49%), North America (34%), Asia-Pacific (14%), Africa (2%), and Latin America (1%). This pattern reflects the distribution of available resources, not the capability or enthusiasm required to perform good research.

This section describes in a systematic way some of the factors that influence diverse medical practices in countries around the world, and more specifically as these practices apply to the management of thyroid cancer. For obvious reasons each of the world's countries cannot be represented and generalisations have been made based upon data provided from representative health-care centres in countries from within each of the major world regions. These countries are shown in Figure 17.1.

17.2. North America

This region consists of the United States of America (USA) and Canada with respective populations of 285.9 million and 30.6 million. These countries contain a diverse mix of ethnic groups predominantly of white European extraction, African Americans and Hispanic ethnicity as well as including indigenous Native American groups. The continent of North America is a vast landmass representing many diverse environments. Despite this the rates of iodine deficiency are very low in North America.

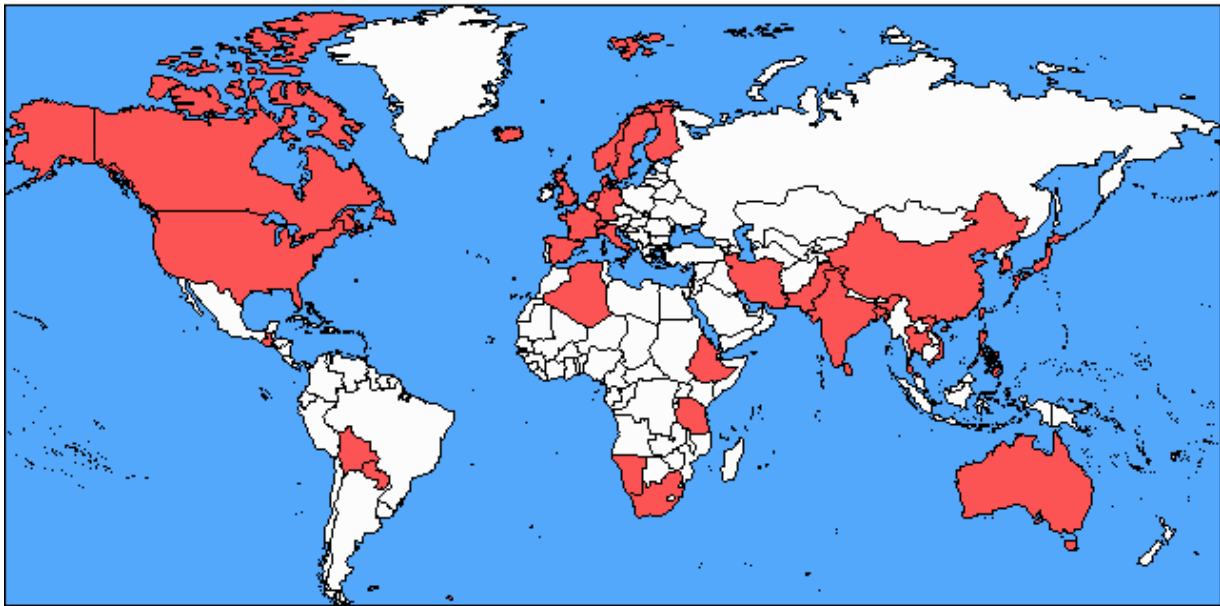


FIG. 17.1. World map indicating the countries (in red) providing details of typical thyroid cancer management.

The incidence of palpable thyroid nodules in the mid 1980s was estimated to be 0.1% per year, and the prevalence between 4-7% [17.2]. In 1999 about 275 000 new thyroid nodules were detected in the USA [17.3]. In the year 1998, in the USA about 17 000 new cases of thyroid cancer were diagnosed, and there were approximately 1200 deaths attributed to thyroid cancer [17.4]. North America generally has a high standard of living. In the USA, however, race and ethnicity are strongly associated with socio-economic status [17.4]. In 1995/6 the percentage of United States (US) population living in poverty included 32% of African Americans and 30.6% of Native Americans [17.5]. Despite the abundance of modern health care facilities, a proportion of the population may have insufficient funds for health insurance plans, and therefore be at risk of inadequate long term management of thyroid cancer.

Comprehensive thyroid cancer management guidelines are established in North America through the National Comprehensive Cancer Network (NCCN) and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) in collaboration with the American Association of Endocrine Surgeons (AAES) [17.6]. Other associations in North America that are involved with education and maintenance of practice standards with respect to thyroid diseases include the American Thyroid Association, Inc., The Endocrine Society, the National Cancer Institute and Thyroid Federation International. The recommendations of these groups, together with groups within Europe, have established standards with respect to diagnosis, treatment and long term management of thyroid cancer that are regarded as the 'bench mark' for care internationally.

A procedure guideline for therapy of thyroid cancer with iodine-131 has been published under the auspices of the Society of nuclear medicine [17.7]. The guideline advocates such therapy for post-operative ablation of thyroid remnants after thyroidectomy and treatment of residual thyroid cancer and metastatic disease after partial or complete thyroidectomy. The recommended post operative ablation dose of iodine-131 is 2.75-5.5 GBq (75-150 mCi), for treatment of presumed thyroid cancer in the neck or mediastinal lymph nodes 5.5-7.4 GBq (75-200 mCi), and for treatment of distant metastases over 7.4 GBq (200 mCi). At higher doses therapy should attempt to limit the estimated radiation dose to bone marrow to less than

2 Gy (200 rad). Also, in the presence of diffuse lung metastases retention of iodine 131 in the body at 48 hours should be less than 2.96 GBq (80 mCi) in order to reduce toxicity. Recombinant human thyroid stimulating hormone (rhTSH), although widely available and approved by the Food and Drug Administration (FDA) for use in diagnostic testing in thyroid cancer, is currently not FDA approved in the United States for use in thyroid cancer therapy [17.7].

17.3. Europe

This region consists of 51 countries with populations ranging from 146.3 million to 25 515. The total population of Europe is 791 million (year 2000 data). The region contains a very diverse range of ethnic groups. Iodine deficiency remains within 31 of the 51 countries, reaching endemic proportions (>10%) in some. Thirteen of these countries have introduced legislation on universal salt iodination [17.8]. Discrimination between iodine deficient areas (IDA) and iodine sufficient areas (ISA) is relevant because it has been shown that the predominant histopathological types of thyroid cancer are different in IDA compared to ISA, with a higher ratio of papillary to follicular cell thyroid carcinoma seen in ISA [17.9]. Some data exist indicating a higher incidence of thyroid nodules, and subsequently a higher incidence of follicular thyroid cancer in iodine-deficient regions [17.10]. In addition, there exists the potential for different responses to ¹³¹I therapy of patients in ISA and IDA.

Marked variation in the incidence of thyroid cancer is seen within Europe. Table 17.1 shows standardized incidence ratios of several European countries for 1990-1994 [17.11]. Statistically significant higher incidences are found in females and males from Iceland compared to most other countries, and high incidences are also found in females from Finland, France, Italy Norway, Switzerland, Spain and Sweden compared to other countries. England, Netherlands, Scotland, Denmark and Germany showed relatively lower thyroid cancer incidences. There is evidence to indicate that the incidence of thyroid cancer is increasing in Scandinavia, England and Wales [17.13]. Despite speculation about the effects of potential widespread low-level radiation to European countries following the Chernobyl nuclear reactor accident of 26 April 1986 in the Ukraine, review of the available data indicates no definite major public health impact outside of the local region [17.12, 17.14].

Due to the disparate cultures and economies of Europe, and in an attempt to unify treatment standards, the European association of nuclear medicine (EANM), through the EANM Radionuclide Therapy Committee, has attempted to survey thyroid cancer therapy throughout Europe [17.15]. Their survey of 23 countries received responses from 20 countries having a combined population of 478 million and 630 centres involved with radionuclide therapy. A total of 1520 isolation beds were available for radionuclide therapy. These were predominantly found in Germany, France, Italy, United Kingdom and the Netherlands. The survey indicated that the level of a single administered ¹³¹I dose that can be administered as an outpatient ranged from 40-1110 MBq (1.1-30 mCi). Licensing, benchmarking and accountability vary greatly throughout the European countries. Although ¹³¹I therapy is mainly administered by nuclear medicine physicians, in Norway any physician is eligible to treat patients with radioiodine, and in Sweden, almost exclusively oncology specialists undertake therapy. In the United Kingdom radiation oncologists and trained endocrinologists were entitled to treat patients with radionuclide therapy in addition to nuclear medicine specialists. This study concluded that more uniform guidelines and legislation are required within the limits of resources available in some countries, and that there is an urgent need for a greater number of isolation beds in dedicated treatment centres throughout Europe.

A similar survey was conducted in the United Kingdom (UK) [17.16]. The authors contacted 354 National Health Service Hospitals and received a 54% response. They estimated a total of 129 centres within the UK that provided radionuclide therapy. Within the responding 50 centres that treated thyroid cancer, a total of 911 patients were treated in 1995. The median waiting time for ¹³¹I therapy was about two weeks. In 1995 approximately 30% of clinicians registered with the Administration of Radioactive Substances Advisory Committee who administer all radionuclide therapy in the UK were haematologists, endocrinologists and rheumatologists. This study highlighted the rising demand for isolation beds and specialist practitioners in the UK [17.17].

TABLE 17.1. STANDARDIZED INCIDENCE RATIOS OF THYROID CANCER FOR SEVERAL EUROPEAN COUNTRIES (after Leenhardt, et al. (2001) [17.12])

Country	Females		Males	
	Incidence/100 000	95% CI	Incidence/100 000	95% CI
Iceland	11.4	8.9-13.9	4.5	3.0-5.9
Finland	6.8	6.4-7.2	2.2	1.7-2.1
France	5.6	5.2-6.1	1.8	1.6-2.1
Italy	5.0	4.5-5.5	2.2	1.9-2.5
Norway	4.7	4.3-5.1	1.6	1.3-1.8
Switzerland	4.6	4.0-5.3	1.8	1.4-2.2
Spain	4.3	3.9-4.7	1.4	1.1-1.6
Sweden	3.6	3.4-3.9	1.4	1.2-1.5
Germany	2.9	2.6-3.3	1.5	1.3-1.8
Denmark	2.2	2.0-2.5	0.8	0.6-0.9
Scotland	2.1	1.9-2.4	0.9	0.7-1.0
Netherlands	2.1	2.0-2.2	1.0	0.9-1.1
England	2.0	1.9-2.1	0.7	0.7-0.8

Note: 95% CI IS THE 95% CONFIDENCE INTERVALS AROUND MEAN VALUES (after Leenhardt, et al., 2001 [17.12])

17.4. Asia-Pacific Region

This region consists of 38 countries with populations ranging from 1.27 billion to 14 166. The total population of the Asia-Pacific Region is 3.46 billion (year 2000 data). Ethnic subgroups include those who have derived from the Indian sub-continent and Middle-East, Chinese and Mongolian ethnicity, Malay and Islander ethnicity and European white populations. A diverse collection of cultures make up the Asia and Pacific Region, each of which may have both direct and indirect influences on the management of thyroid cancer.

Australia

This island continent of 7 682 300 square kilometres has a population of 18.7 million with a relatively high inter-ethnic mix, but predominantly consisting of those derived from white European ethnicity. Over one million immigrants have settled in Australia over the past 50

years. Due to environmental constraints, the population is mainly found in coastal regions, with the largest populations on the eastern coast. There is no endemic dietary iodine deficiency. The gross National product (GDP) is AU \$165 billion, and 8.5% of the GDP is spent on healthcare [17.18]. Tax-based revenue provides health care by public hospitals. Private health insurance is also available for those who prefer private hospital care.

Cancer deaths account for 27.8% of total mortality. The overall incidence of thyroid cancer in Australia is approximately 5.5/100 000 population. In the state of New South Wales (NSW) the incidence of thyroid cancer in 1999 was 2.9/100 000 for males, and 8.9/100 000 for females, and age-standardized mortality from thyroid cancer for 1999 were 0.2/100 000 for males and 0.4/100 000 for females. Of the many ethnic groups within Australia, those of Middle East and Asian origin have statistically significant higher age-standardized incidence rates of thyroid cancer compared to the overall incidence rate [17.19, 17.20].

Management of thyroid cancer in Australia is usually a collaborative effort between thyroid surgeon, endocrinologist and nuclear medicine physician. The nuclear medicine physician manages ^{131}I therapy. Currently, there are 130 nuclear medicine specialists in Australia, with a nationwide range of 42 000 to 304 000 adults per nuclear medicine physician [17.21]. Nuclear medicine physicians are Fellows of the Royal Australasian College of Physicians having undertaken specialty post-graduate training in internal medicine and then three years of additional training in nuclear medicine. Radiologists may also practice nuclear medicine in Australia if they complete two years of nuclear medicine specialty training supervised by the Royal Australian and New Zealand College of Radiologists.

Patients most typically present to a family practitioner for investigation of a thyroid mass. Alternatively, a suspicious nodule is detected during the course of other medical imaging investigations. The patient will usually be investigated by $^{99\text{m}}\text{Tc}$ thyroid scintigraphy. Thyroid ultrasound may also be performed at this time or used to assist fine needle aspiration biopsy of the mass. Patients with a histological confirmed diagnosis of thyroid cancer or strong clinical suspicion of thyroid cancer are usually referred for surgical opinion. The surgeon may perform a single total thyroidectomy procedure or a two-stage thyroidectomy. Patients with differentiated thyroid cancer will then undergo ^{131}I ablation therapy under the supervision of a nuclear medicine physician. This is usually performed within an isolation ward of a public or private hospital. Design guidelines have been developed for ^{131}I therapy facilities in NSW for the NSW Hospital and University Radiation Protection Officers Group (HURSOG) [17.22]. A designated Radiation Protection Officer usually undertakes the supervision of radiation safety issues. The maximum activity of ^{131}I at which a patient may be discharged from hospital in Australia is less than 600 MBq (16.2 mCi). This approximates a dose rate of $25\mu\text{ Sv/hour}$ at one metre, given shielding by the patient's body [17.23]. ^{131}I is locally produced and supplied from Australia's only nuclear reactor at Lucas Heights near Sydney, NSW. Alternatively, ^{131}I can be imported from overseas sources but may be more expensive. The ^{131}I is available in liquid or capsule form. The most common practice in Australia is to administer ^{131}I in capsule form for doses required to treat thyroid cancer. The typical cost of a 4 GBq (108 mCi) capsule or solution is US \$155 plus transport costs.

Preparation for ^{131}I therapy usually involves cessation of post-thyroidectomy thyroxine replacement and introduction of triiodothyronine (T3) for a period of 2-4 weeks. All thyroid hormone replacement is ceased for a further 2 weeks prior to radioiodine therapy. Although recombinant thyroid stimulating hormone (rhTSH) is available, its high cost is a deterrent for use in Australia. Initial post thyroidectomy ^{131}I scanning is commonly omitted due to

concerns about stunning [17.24]. Following administration of radioiodine, the patient remains in isolation until the gamma radiation levels drop to below 600 MBq (16.2 mCi) equivalent. After this time the patient may be discharged home with instructions regarding radiation safety aimed to minimize exposure to gamma radiation of other household members and the general public.

Patients are generally monitored by serum thyroglobulin measurement and clinical assessment at 3-6 monthly intervals early in the post therapy course. Low-dose ^{131}I or ^{123}I WBS also may be performed to confirm thyroid ablation. Most laboratories also measure anti-thyroglobulin antibodies with appropriate dilutions. Where there is a suspicion of disease recurrence, the patient may be further investigated by low-dose ^{131}I whole-body scan (WBS) or alternatively, ^{123}I WBS. Where a higher suspicion of disease recurrence exists, the patient may undergo further high dose ^{131}I therapy followed by ^{131}I WBS. Where de-differentiation of differentiated thyroid cancer is suspected or clinical discordance with ^{131}I scan findings and serum thyroglobulin levels, ^{18}F fluoro-deoxy-glucose (FDG) positron emission tomography (PET) scan or $^{99\text{m}}\text{Tc}$ sestamibi whole body scan may be performed to assess extent and location of disease. The availability of FDG PET scan is currently somewhat limited in Australia, although beginning to expand nationwide.

Some Australian hospitals also assist in the management of thyroid cancer patients from neighbouring Pacific Islands. New Caledonia is one such example. New Caledonia is a French island territory in the Pacific Ocean with 200 000 inhabitants. Since 1985 there has been a trend of increasing incidence of thyroid cancer in this population. In 1985 the average annual incidence of thyroid cancer in New Caledonia was 5.8/100 000, in 1992 it was 10.8/100 000, and in 1996 it was greater than 20/100 000 [17.25]. Female Melanesians have an annual thyroid cancer incidence of 35/100 000, one of the highest worldwide [17.26]. These patients are diagnosed and operated upon in New Caledonia. However, due to the lack of a nuclear reactor and nuclear medicine facilities, they receive thyroid ablation, low-dose ^{131}I WBS and ^{131}I therapy in Australia [17.27].

Bangladesh

The People's Republic of Bangladesh is a country of 147 570 square kilometres area containing 123.8 million people. Economically it is regarded as a developing country and has a mean annual per capita income of 5955 Taka (US \$131.5). The proportion of the total annual budget spent on healthcare is 5.3%. The country averages 25 physicians per 100 000 population. Bangladesh has 30 colleges providing undergraduate medical education, 6 colleges providing post-graduate education and 1 providing post-graduate education in nuclear medicine. Nuclear medicine is an independent speciality that is not affiliated to other specialties such as radiology, endocrinology or internal medicine. In addition, 9 medical institutions offer non-academic post-graduate medical education and training in nuclear medicine. Nuclear medicine physician training is often supplemented by overseas experience in Europe, USA or Asia. In the absence of structured local training, overseas training is also required for nuclear medicine technologists, medical physicists and radio-pharmacists. Currently there are 80 qualified nuclear medicine physicians in Bangladesh, 70 nuclear medicine technologists, 28 medical physicists and 5 radio-pharmacists. The country has 21 gamma cameras including 8 SPECT-capable cameras. A total of 10 thyroid probes are available. Endemic dietary iodine deficiency remains a problem throughout a large proportion of Bangladesh. In a country where coronary artery disease, diabetes and geriatric diseases are regarded as the major health problems, and cancer ranked fourth, thyroid cancer is the fourth

most prevalent cancer in women. Some ^{131}I is locally available for therapy but most is imported.

China

China is a vast country covering 9 526 900 square kilometres and containing 1 259 million people. Although there are 56 different ethnic groups within China, the Han group comprises 94%. Some regions of China have up to 30% of the population affected by endemic goitre due to iodine deficiency. Overall the mean incidence is 10%. Cardiovascular disease is the leading cause of death, followed by cancer. The incidence of thyroid cancer in China is 1.2/100 000 in males, and 2.9/100 000 in females. Mortality from thyroid cancer is 0.38/100 000 in males and 0.73/100 000 in females.

There are about 15 nuclear medicine facilities within China that treat thyroid cancer, each with modern gamma cameras and isolation wards. The three largest centres are the Chinese Academy of Medical Sciences and Peking Union Medical College, West China University Medical College and the Shanghai Sixth People's Hospital. Basic medical training in China is 5-8 years with or without post-graduate medical specialty training. A radiation licence is required to treat patients with radioiodine. The maximum annual radiation dose allowed for the general public in China is <1 mSv, for individual carers <50 mSv, for family infants <1 mSv and the maximum post ^{131}I therapy hospital discharge dose is <400 MBq. The legal limit of ^{131}I administered to an outpatient is 1110 MBq (30m Ci). For radioiodine therapy of thyroid cancer, treatment doses range from 1100 MBq (30 mCi) to 7.4 GBq (200 mCi). For simple thyroid ablation commonly a dose of 3.7 GBq (100 mCi) is given, for treatment of cervical lymph node metastases 3.7-5.5 GBq (100-150 mCi) is given, for lung metastases 5.5 GBq (150 mCi), and for bone metastases 7.4 GBq (200 mCi).

Most patients with well-differentiated thyroid cancer are referred to nuclear medicine physicians by head and neck surgeons for radioiodine therapy. Other health professionals do not treat patients with radioiodine. High-risk patients are referred having undertaken near-total thyroidectomy. Those patients considered at lower risk may also have a similar operation but if the patient refuses radioiodine therapy, more commonly sub-total thyroidectomy or total lobectomy is undertaken. Endocrinologists tend to be involved only in the management of benign thyroid disease. Patients with bone metastases and bulky mediastinal node disease are treated with external beam radiotherapy by radiation oncologists, and patients with anaplastic and medullary thyroid carcinomas are treated by chemotherapy by medical oncologists.

Typically, a patient presenting with a neck mass suspicious for thyroid cancer will be investigated by physical examination, thyroid ultrasound, $^{99\text{m}}\text{Tc}$ pertechnetate thyroid scan, biochemical thyroid function tests and serum calcitonin levels. If imaging demonstrates a solid and cold nodule/mass, fine needle aspiration biopsy (FNAB) is performed. Patients with 'warm' nodules or benign FNAB results have clinical follow-up. The average cost to treat thyroid cancer patients with radioiodine in hospital is US \$800 (US \$130 to US \$250 per day). The mean duration in hospital is 4 days. If the patient is employed the burden of cost is between 0-50% of this amount. In some regions, where the patient is unemployed or uninsured, the patient pays the full cost. In China the burden of health care costs are borne by health insurance companies, the Government and the private individual. The cost of the ^{131}I is US \$2 per 37MBq (1 mCi) in liquid form, and US \$3-6 per 37 MBq (1 mCi) in capsule form. There are three main suppliers of ^{131}I for therapy in China, the Chinese Isotope and Atomic Energy Institute, Sichuan Atomic Energy Institute and a private radiopharmaceutical supply company.

Patients usually receive ^{131}I therapy 1-3 months after surgery. Typically, exogenous thyroxine replacement is discontinued 5-6 weeks prior to the scheduled date of therapy and replaced by T3 for 3 weeks. T3 is ceased 2-3 weeks before ^{131}I therapy. Recombinant thyroid stimulating hormone (rhTSH) is not readily commercially available in China, and costs also prohibit its widespread use. For post therapy surveillance, ^{131}I WBS is performed using a typical scanning dose of 110-185 MBq (3-5 mCi). Patients are prepared by cessation of exogenous thyroxine replacement 5 weeks prior to the scan date. T3 replacement therapy is introduced, and continued until 2 weeks prior to the scan date. Serum thyroglobulin measurement is also available in China at a cost of US \$5-7 per sample. Measurements are made dependent upon the course of follow-up, averaging every 6-12 months. A pre- ^{131}I therapy serum thyroglobulin measurement is routinely taken 1-3 months after thyroid surgery. The measurement of anti-thyroglobulin antibodies is available at some but not all hospital laboratories. The usual post-therapy follow-up protocol consists of patient review at 1-3 months after ^{131}I therapy. This is mostly successful but some patients are lost to follow-up due to the usual reasons related to changing address and location. This problem is, however more severe in patients living in the more remote regions where adequate communication may be problematic.

In the larger cities of China, ^{18}F FDG is used for PET imaging of suspected metastatic disease where patients have a negative ^{131}I WBS and a rising serum thyroglobulin level. FDG PET imaging is also used where the patient is unwilling to withdraw from thyroxine replacement hormone and requires re-staging. For those patients who cannot afford FDG PET imaging, (approximate cost US \$1000), or where PET services are not available, patients may be investigated by $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl whole body imaging. ^{123}I imaging is not used in China. China has a growing number of physicians becoming familiar with the appropriate therapy and follow-up protocols for thyroid cancer. This aids the maximum number of patients receiving the appropriate therapy and the best possible utilization of resources. However, in poorer remote regions such services are still not available to all patients and poverty may preclude therapy or prevent patients having much needed repeat ^{131}I . Although resources are good in the larger centres, a nation of such a large size has far too few resources available for, both the detection and diagnosis of thyroid cancer, as well as its treatment. In China today there are ongoing education programs for physicians related to the management of thyroid cancer patients. National meetings on thyroid cancer are held twice each year and there are centres conducting active research in the field of thyroid cancer.

India

This diverse and expansive country has a population of approximately 1 billion. The country is also culturally diverse with a mix of religious groups including Hindu, Muslim, Christian, Parsi, and Buddhists. Throughout India the general perception of illness, and consequent medical compliance, relates to income levels. The majority of people are of middle income, up to 30% of the population live below the poverty line and 2-5% are considered wealthy. High levels of endemic goitre remain in India, particularly in the sub-Himalayan regions, where up to 30-40% of the population may be affected. On a national basis, however, endemic goitre has been significantly reduced due to a vigorous national iodination program, but remains at 8-16% overall.

Until 1997, only three nuclear medicine centres were adequately set-up for radioiodine therapy of thyroid cancer patients. By 2002 there were 15 centres, all equipped with modern gamma cameras and isolation wards complying with radiation regulations. Basic medical training is for 6 years including a six-month 'house-post' period. Formal specialist training in nuclear medicine is required in order to obtain radiation licensing. There are 12 thyroid cancer

registries established in India that provide important epidemiological data. The age-adjusted incidence of thyroid cancer in India per 100 000 population on a regional basis, is between 0.2-1.7 for males and 0.4-5.1 for females. Patients with a suspicious neck mass are most often referred to a nuclear medicine specialist from general physicians, surgeons, endocrinologists or oncologists. Typically, these patients are investigated by thyroid scintigraphy, thyroid ultrasound and FNAB. Upon diagnosis of thyroid cancer, the patient is referred to an appropriate surgeon who performs a near-total thyroidectomy. Post-surgery low-dose ^{131}I WBS is often used to check the adequacy of such surgery.

The daily cost of hospital care for thyroid cancer patients is approximately US \$100. Most commonly, the patient meets this cost personally since few people have medical insurance. The government does, however, provide free basic health care for poorer patients. Patients are prepared for radioiodine therapy over a 4-6 week period by withdrawal of thyroxine supplementation. T3 is not widely available in India and therefore, is only used in specific situations, where available. Due to the high cost, rhTSH is not used in India. The liquid form of iodine-131 is most commonly used for therapy. For ablation of residual thyroid tissue, doses of 1.85-3.7 GBq (50-100 mCi) are used. Metastatic disease within lymph nodes is treated with 5.55 GBq (150 mCi). Metastatic disease with the lungs is also treated with this same dose. Metastatic disease within bone and bone marrow is treated with doses of 9.25-11.1 GBq (250-300 mCi). ^{131}I is available from the Indian Atomic Energy Department. In India the legal maximum outpatient dose of ^{131}I is 555 MBq (15 mCi), and this is also the equivalent limit for discharge from hospital post-radioiodine thyroid cancer therapy ($\leq 25 \mu\text{Sv/h}$ at 1 metre). Indian regulations state that the maximum annual radiation dose for the general public should be less than 2 mSv, and for individual carers less than 5 mSv. Patients routinely have ^{131}I WBS performed post therapy.

Patient follow-up is performed by clinical assessment as well by monitoring serum thyroglobulin levels at six month intervals. Low-dose 150-185 MBq (4-5 mCi) ^{131}I WBS is also performed. If there is no evidence of metastatic disease seen on WBS and serum thyroglobulin remains normal, annual WBS is performed after 3 years, and thereafter every 5 years. Patients routinely have an annual clinical examination, serum thyroglobulin estimation and chest X ray. Following this, serum thyroglobulin is the mainstay of follow-up. This test is widely available and cost about US \$10 per sample. Anti-thyroglobulin antibody levels are routinely measured. For all follow-up ^{131}I WBS the patient ceases thyroxine hormone replacement therapy for 4-5 weeks and avoids iodine-containing foods. Other imaging modalities such as $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl WBS are widely available. FDG PET imaging is only available at few centres and ^{123}I is currently not available in India. Follow-up is generally successful, with about 90% of patients complying with follow-up. Economic and distance factors account for the remaining non-complying patients. India has a well-established treatment program for thyroid cancer patients, and by the sheer volume of the population, by world standards a large number of patients are diagnosed, treated and registered for follow-up.

Islamic Republic of Iran

This Islamic middle-eastern country has a population of approximately 65 million. Although only 46% of the population are Persians, this group is culturally dominant. Other ethnic groups include Azeris (17%) and Kurds (9%), as well as smaller groups including Gilaki, Mazandarani, Lur, Bakhtiari, Arabs and Baloch. Iran has modern health care and education facilities in the larger cities, and an excellent health network in the rural regions. According to the 1996 census, 84.7% of males and 74.2% of females aged >6 years are literate. The Iranian

economy is principally based upon oil, other natural resources and the manufacturing industry.

Iran covers an area of 1 633 188 km². There are forests in the north and west but desert dominates the central regions and semi-arid country is found in the east and south. Iran is very mountainous, with all the larger cities found at altitudes greater than 1 000 metres above sea level. Prior to 1992, mild to moderately severe iodine deficiency was estimated to affect 20 million people in Iran. A national salt iodisation program has achieved a greater than 90% success based upon median urinary iodine concentrations in all provinces greater than 10 µg/dl. The estimated prevalence of thyroid cancer is 295/100 000 in Iran, although this may be an overestimate since no accurate National Registry Cancer data is available.

Thyroid cancer is treated in seven nuclear medicine centres in Iran, including five in Tehran (three government and two private facilities), one in Isfahan and one in Shiraz. These centres all have SPECT capable gamma cameras, and modern isolation wards. The average cost per day in a government-funded hospital for an uncomplicated thyroid cancer patient is US \$12.50, and the average cost for thyroidectomy is US \$150. Costs are higher in the private hospitals. Patients employed in government jobs, generally have government-funded health insurance coverage which reduces personal costs by 80-100%. People otherwise employed can have private health insurance that provides free health care in private health care facilities. In addition, there are a few public-funded organizations that provide health care support for patients with certain chronic diseases, including cancer.

In the larger cities endocrinologists and internists are the main referrers of patients, and they also manage the ongoing care of the patients after surgery and radioiodine therapy. Only nuclear medicine physicians treat with radioiodine. Nuclear medicine physicians, having completed the 7-year undergraduate medical degree course provided by the Iran Ministry of health and medical education, enter a nuclear medicine residency program for an additional 3 years of post-graduate training. Following the completion of training, the Iran Atomic Energy Organization (IAEO) licenses specialists. A typical clinical work-up for a suspicious clinically non-toxic neck mass includes a FNAB, with or without TSH, free thyroxine measurement and thyroid ultrasound. Upon the histological diagnosis of differentiated thyroid cancer, the surgeon performs a unilateral thyroid lobectomy and isthmus excision if the primary cancer is less than 1 cm in diameter and confined to one lobe. Where the primary cancer is larger, and/or there is evidence or strong suspicion of extra-thyroidal extension or metastatic spread, or a history of previous radiation exposure to the head and neck region, a near-total thyroidectomy is performed. This may include lymph node dissection and resection of metastatic disease where appropriate.

In preparation for ¹³¹I therapy, patients stop thyroxine therapy for 4 weeks prior to treatment, or convert from thyroxine to T3 for 2-3 weeks before discontinuing all thyroid hormone replacement for another 2-3 weeks before treatment. The aim is for the thyroid stimulating hormone level to be greater than 25 mU/L. Patients have a baseline serum thyroglobulin measurement and WBS using 74-185 MBq (2-5 mCi) ¹³¹I before ¹³¹I ablation therapy. A low iodine diet is advised for 1-2 weeks before scanning. The rhTSH is currently not available for use in Iran. The therapy dose range of ¹³¹I given to thyroid cancer patients in Iran is 1.1-11.1 GBq (29.9-300 mCi). ¹³¹I therapy is administered in liquid form, and obtained from IAEO or imported from England. The dose selected depends upon the clinico-pathologic staging, post surgery scan and serum thyroglobulin level. The average empiric dose is 3.7 GBq (100 mCi). The average cost of a single dose (1.85-11.1 GBq) is US \$50-110 in the government hospitals or US \$65-170 in the private hospitals. The maximum permissible

outpatient dose of ^{131}I is 1.1 GBq (29.9 mCi). The IAEA recommendations base the management of radiation dose limits and levels on the recommendations of the International Commission on Radiological Protection [17.28, 17.29].

Patient follow-up by WBS is performed annually until two successive scans are negative. After this time WBS is only performed where there is an increase in serum thyroglobulin levels or where there is clinical evidence of disease progression. WBS uses a low ^{131}I dose (74-185 MBq) with scanning 48-72 hours later. Initial post ^{131}I therapy follow-up is at 4-6 weeks. Serum thyroglobulin levels are usually measured every 6 months during the first few years after surgery, and then annually lifelong. The laboratories usually measure anti-thyroglobulin antibodies and do appropriate dilutions only if requested by the physician. Unfortunately, many patients are lost to follow-up in Iran, mostly due to economic reasons and a lack of education about the need for follow-up. Patients followed-up who have negative WBS but rising serum thyroglobulin levels can be imaged with $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl whole body imaging but FDG PET imaging is not available in Iran. Although ^{123}I can be produced locally it is currently not used due to relatively high costs.

Japan

This group of islands of total area 370 000 square kilometres has a population of 127 million. This population comprises predominantly Japanese ethnicity. There is a high dietary intake of sea-foods including seaweed and its related products. Consequently, there is virtually no iodine deficiency in Japan.

There are approximately 60 nuclear medicine facilities within Japan equipped with modern gamma cameras and isolation wards suitable for thyroid cancer therapy. The incidence of thyroid cancer in Japan is 1.9/100 000 for males and 8.7/100 000 for females. The mortality from thyroid cancer is 0.6/100 000 for males and 1.2/100 000 for females.

The major referrers of patients with thyroid cancer for radioiodine therapy are surgeons, endocrinologists and oto-rhino-laryngologists. Generally, nuclear medicine physicians administer radioiodine therapy, although in a few institutions, radiation oncologists may do this. The role of the surgeon is to perform the thyroidectomy operation, and endocrinologists are involved in both the diagnostic work-up and may prescribe thyroid hormone replacement for some patients. Medical and radiation oncologists generally have little role in management of patients with thyroid cancer. Typically, a nuclear medicine specialist has 6 years of basic medical training and 3-5 years of specialty training. No specific radiation licence is required. Japan has a public or government funded health care program. Patients generally are required to pay between 20-30% of their health care costs after hospital admission for treatment of thyroid cancer. A typical diagnostic work-up of a patient with a neck mass suspicious for thyroid cancer includes thyroid ultrasound guided fine-needle aspiration biopsy. Upon diagnosis, hemithyroidectomy with neck dissection is performed routinely. Those patients with clinically detected distant metastases, multi-focal disease within the gland, local extra-thyroidal tumour spread, tumour involving the isthmus or contralateral lobe or extensive nodal disease, have a total thyroidectomy procedure. For preparation for ^{131}I therapy, thyroxine replacement therapy is replaced by T3 hormone replacement therapy for 2 weeks. All thyroid hormone replacement therapy is ceased for 2-3 weeks prior to ^{131}I therapy. The use of rhTSH is currently under clinical trial in Japan.

The legal limit of a single ^{131}I dose administered to an outpatient is 500 MBq. For thyroid cancer 2-7 GBq (60-180 mCi) is used, with the modal dose of 3.7-4.4 GBq (100-120 mCi).

The maximum allowable post ^{131}I therapy hospital discharge dose is 500 MBq or 30 $\mu\text{Sv}/\text{hour}$. The cost of a 3.7 GBq (100 mCi) capsule is about US \$1000. There is a sole private supplier of ^{131}I in Japan. Two to four weeks following ^{131}I therapy patients are reviewed. It is rare for patients to be lost to follow-up in Japan. A well-organized follow-up and patient notification system is available to minimize the likelihood of follow-up failure. Serum thyroglobulin measurement is readily available in Japan and costs about US \$25 per sample. Pre- ^{131}I thyroglobulin levels are routinely measured around the time of referral for ^{131}I therapy. Anti-thyroglobulin antibody levels are also routinely measured incorporating appropriate dilutions in most laboratories. Post ^{131}I WBS is performed as well as low dose ^{131}I surveillance imaging using 37-110 MBq (1-3 mCi) doses. Patients are prepared for scanning in a similar fashion to the preparation for ^{131}I therapy. FDG PET whole body imaging is becoming more readily available for use as a staging instrument and $^{99\text{m}}\text{Tc}$ sestamibi and ^{201}Tl whole body imaging are currently widely available throughout Japan. ^{123}I is also widely available and ^{123}I WBS widely utilized. It is envisaged that rhTSH will become available and widely used in Japan. The current major limitation is regarded as being a relative shortage of isolation wards.

Pakistan

The country of Pakistan comprises four provinces (North West Frontier Province, Punjab, Sindh and Balochistan), tribal areas Azad Kashmir and the Federal Capital with a total area of 796 096 square kilometres. The total population as estimated at the 1998 census is 130 579 571 with an average annual growth rate of 2.61%. There are four major ethnic groups: the Pathans, Punjabis, Sindhis and Balochis. More than 50% of the population lives in rural areas where there is a low literacy level and relative isolation from tertiary health care units. High rates of endemic iodine deficiency are seen in the northern and western mountainous areas.

Health care in the fields of radiotherapy and nuclear medicine are mainly provided by the Pakistan Atomic Energy Commission (PEAC) and only by a few hospitals in the private sector. Consequently, the majority of patients with thyroid cancer are treated at PEAC medical centres. Institutions in the North Western Frontier Province such as the Institute of Radiotherapy and nuclear medicine at the provincial capital, Peshawar, also provide care to a large number of refugees from neighbouring Afghanistan. Currently there are 12 PAEC medical centres with modern nuclear medicine facilities, most of which provide radioiodine therapy.

In Pakistan patients with a suspicious neck lump are seen by general practitioners, and are usually investigated by $^{99\text{m}}\text{Tc}$ pertechnetate scintigraphy. If a suspicious hypo-functioning nodule is identified, the patient is investigated by fine needle aspiration biopsy. If thyroid cancer is confirmed, the patient is referred to a general surgeon or ear, nose and throat surgeon for near-total thyroidectomy. The patients are subsequently referred to nuclear medicine physicians for radioiodine therapy. Endocrinologists have a minimal role in the management of thyroid cancer. Medical and radiation oncologists are only involved in the management of undifferentiated and medullary cell thyroid cancers.

Basic medical training in Pakistan is 6 years and, after an additional 2 years, a further 5 years of training is required for specialisation in nuclear medicine. Nuclear medicine specialists require a radiation licence that is regulated by the Pakistan Nuclear Regulatory Authority (PNRA). Health care in Pakistan is means tested. Those with a monthly income less than US \$83 receive free government sponsored health care. Those patients with differentiated

thyroid cancer who earn above this monthly limit are expected to pay the cost of the ^{131}I dose (US \$16.67).

Radioiodine is usually administered 6 weeks after thyroid surgery. Preparation of patients for radioiodine therapy includes withdrawal of thyroxine replacement therapy for 4-6 weeks. At the time of writing T3 is not available in Pakistan. rhTSH is also not available and is also prohibitively expensive. ^{131}I is dispensed in liquid form and is produced and supplied by the Radioisotope Production Group of the PINSTECH (Pakistan). The legal limit of a single radioiodine dose that can be administered as an outpatient is 1100 MBq (30 mCi). The usual dose range is 925 MBq (25 mCi) to 7.4 GBq (200 mCi), where 1.85-3.7 GBq (50-100 mCi) is given for thyroid remnant ablation, 5.55 GBq (150 mCi) for local involvement and 7.4 GBq (200 mCi) for distant functional metastases. In Pakistan the maximum annual radiation dose for the general public is 1 mSv, for individual carers 20 mSv and for family infants <1 mSv. The maximum allowable post ^{131}I therapy hospital discharge dose is 1.10 GBq (30 mCi) if the patient travels home by private transport and 555 MBq (15 mCi) if travelling by public transport.

Whole body ^{131}I scanning is performed after therapy and also where appropriate for further follow-up. Iodine 123 is not available in Pakistan. Patients are prepared for low-dose (74-185 MBq or 2-5 mCi) ^{131}I WBS by cessation of thyroxine hormone replacement for about 6 weeks and a low iodine diet. Post ^{131}I therapy follow-up with ^{131}I WBS is generally performed at 6 months. If the scan is negative, further follow-up is at 2 years then 5 yearly intervals. The patients are also followed by 6-12 monthly measurement of serum thyroglobulin at the government-subsidized cost of US \$2.92 per sample. A pre-radioiodine measurement is not routinely taken. Anti-thyroglobulin antibodies are not measured routinely. The rate of patients follow-up is low. Those who are lost include those of low income and education that live remote from the treating medical centre. Although FDG PET imaging is not generally available, staging imaging of non-iodine avid disease can be performed using whole body $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl imaging.

Although Pakistan has limited resources, most of its nuclear medicine centres are modern and well equipped with appropriate isolation rooms for radioiodine therapy. Furthermore, Pakistan has self-sufficiency in the supply of radioiodine for therapy and the PAEC plans to establish additional new nuclear medicine facilities. In addition, the Pakistan Institute of engineering and Applied Sciences (PIEAS) and the College of Physicians and Surgeons of Pakistan (CPSP) offer post-graduate degree training in nuclear medicine.

Philippines

The Philippines comprise 7100 islands with a land area of about 300 000 square kilometres. Its 76.5 million inhabitants consist predominantly of Christian and Muslim Malay ethnicity. Despite the geographic features, the Philippines islands have a high rate of endemic iodine deficiency, reaching as high as 20% in mountainous regions. The average annual per capita income is about US \$3000 and widespread poverty remains a problem for adequate health-care delivery.

There are 16 nuclear medicine facilities in the Philippines, 14 of which have modern gamma cameras, and most have appropriate isolation wards for radioiodine therapy. Apart from facilities on the islands of Cebu and Davao, these centres are located in and around Manila on the island of Luzon. Private health care insurance is growing in the Philippines as there is only limited government subsidisation of health care costs. For treatment of thyroid cancer,

where private health insurance is unavailable, the patient pays for almost the total cost. The average bed-stay cost per day of hospital admission is US \$50.

For the period of 1980-1992, the combined age-standardized incidence rates for thyroid cancer were 2.6/100 000 for males and 7.9/100 000 for females. Thyroid cancer was ranked seventh overall in incidence (males 18th, females 4th) of all cancers in the population [17.30]. In 1998, an estimated 2068 females and 516 males had differentiated thyroid cancer, comprising 3.7% of all cancers [17.30]. The mortality rate for thyroid cancer ranges from 2-4% and the recurrence rate is 6.3% [17.30]. Some of the world's highest incidences of thyroid cancer among both men and women have been observed among Philippine migrants to Hawaii, Los Angeles and San Francisco, as well as native Hawaiians and residents of French Polynesia and the Philippines [17.31-17.34].

Patients are generally referred from general practitioners to nuclear medicine physicians and endocrinologists for diagnostic work-up and management. A typical diagnostic work-up of a suspicious thyroid mass consists of biochemical thyroid function testing, thyroid imaging with ^{99m}Tc pertechnetate scintigraphy and thyroid ultrasound followed by fine needle aspiration biopsy. General surgeons and occasionally ear, nose and throat surgeons perform near total thyroidectomy, subtotal thyroidectomy or, less frequently, thyroid lobectomy operations. Either a nuclear medicine physician or endocrinologist administers radioiodine therapy. In the Philippines, the role of medical oncologists is limited to patients with undifferentiated thyroid cancer, and radiation oncologists are involved in the management of patients with non-iodine avid metastatic disease, particularly where there are compressive symptoms. Basic medical training in the Philippines consists of 10 years and post-graduate medical specialty training consists of an additional 3-4 years of residency in nuclear medicine or a combination of 2 years of internal medicine or pathology and 2 years of nuclear medicine. A radiation licence is required and is issued following completion of a prescribed Radiation Techniques and Training Course from the national regulatory body (Philippine Nuclear Research Institute).

Typically patients are treated with radioiodine 4-6 weeks after surgery. Thyroxine therapy is withdrawn from the patient for 4 weeks. The cost of T3 often prohibits its use, and also is generally not widely available in the Philippines. All thyroid hormone replacement is ceased for 2 weeks prior to radioiodine therapy. Similarly, rhTSH is not used since its local cost is US \$1000 and it is not locally available. In the Philippines the legal limit of a single ^{131}I dose that can be administered as an outpatient is 555 MBq (15 mCi). For thyroid cancer a typical standard ^{131}I dose for the treatment of residual neck thyroid tissue is 3.7 GBq (100 mCi), although lower doses in the range of 1.85-2.2 GBq (50-60 mCi) are also used. For lung metastases 5.5 GBq (150 mCi) is used and for bone metastases 7.4 GBq (200 mCi) is used. Liquid ^{131}I is used more often than ^{131}I capsules due to the lower cost. The cost of 3.7 GBq liquid ^{131}I is US \$200 compared to US \$220 for 3.7 GBq ^{131}I capsule. There are at least four international companies that supply radioiodine to the Philippines but despite this, supplies are often still difficult to obtain.

The maximum annual permissible radiation dose for the general public in the Philippines is 1 mSv. The maximum annual radiation dose for individual carers is 1 mSv and the maximum post ^{131}I therapy hospital discharge dose is less than 25 $\mu\text{Sv}/\text{hour}$ at 1 meter distance. Following ^{131}I therapy the patient is first reviewed at 2 weeks. Mainly due to geographic and financial reasons about 50% of patients are lost to follow-up. Serum thyroglobulin measurement is available at a cost of US \$30 per sample. Typically, this is measured every 6-12 months. Where the patient can afford the cost, a pre- ^{131}I serum thyroglobulin measurement is

taken 4-6 weeks after surgery. Only a few laboratories routinely measure anti-thyroglobulin antibody levels.

New cases of differentiated thyroid cancer are commonly investigated by low dose (37 MBq or 1 mCi) 48-72 hours ^{131}I WBS prior to ^{131}I therapy. Where bulky thyroid remnants are present, the patient undergoes additional surgery prior to ^{131}I therapy. Not all patients undergo post-therapy ^{131}I WBS. Those patients who have follow-up ^{131}I WBS (185 MBq or 5 mCi) are prepared by a similar protocol before therapy, and are advised to avoid iodine rich foods 5-7 days prior to the scan. Iodine-123 is not available in the Philippines. As of January 2002 whole body FDG PET imaging is available in Manila, and whole body imaging with $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl is readily available for investigation of non- ^{131}I avid disease.

Republic of Korea

The Republic of Korea has a population of 45 million and a land area of 90 000 square kilometres. This population is almost entirely of Korean ethnicity. A patient's perception of illness and reasons for non-compliance may relate to Confucianism. There is no endemic iodine deficiency.

The incidence of thyroid cancer in the Republic of Korea is 1.5/100 000 for males and 8.1/100 000 for females. There are 15 major hospitals with a total of 250 gamma cameras and 25 isolation wards suitable for thyroid cancer therapy. The average bed stay cost for each thyroid patient is US \$200/day. Most commonly, patients will have to pay 20% of this amount. There is one semi-government funded medical insurance program, dependent upon income levels, where low-income earners receive free health care.

In the management of thyroid cancer patients, only nuclear medicine physicians administer Iodine-131 therapy. The role of the surgeon is limited to surgery, and the endocrinologist is involved in the follow-up of patients after operation. Medical and radiation oncologists generally have little role in the care of thyroid cancer patients in the Republic of Korea. A nuclear medicine specialist in the Republic of Korea has typically completed 6 years of basic medical training before undertaking 4 years of specialty training. All nuclear medicine physicians require a radiation licence. A typical diagnostic work-up of a suspicious neck mass includes thyroid ultrasound, fine needle aspiration biopsy for cytology, and sometimes $^{99\text{m}}\text{Tc}$ pertechnetate thyroid scintigraphy. Following diagnosis, the most commonly performed surgical procedure is near total thyroidectomy. ^{131}I therapy typically takes place 2-3 months after surgery. The patient is prepared by withdrawal of thyroxine and substitution of T3 hormone replacement for 4 weeks. All thyroid hormone replacement is ceased for 2 weeks prior to ^{131}I therapy. Although rhTSH is available, its cost is considered prohibitive.

The legal limit of outpatient ^{131}I therapy in the Republic of Korea is 1100 MBq (30 mCi). For thyroid cancer 5.5-7.4 GBq (150-200 mCi) doses are most commonly used. Capsules are generally used at a cost of US \$600 each from a domestic supplier (KAERI). The average total dose range of ^{131}I given to thyroid cancer patients in the Republic of Korea is 3.7-14.8 GBq (100-400 mCi). In South Korea the maximum permissible annual radiation dose for the general public is 1 mSv, the maximum annual radiation dose for individual carers is 20 mSv and the maximum post ^{131}I therapy hospital discharge dose is 1100 MBq (30 mCi). ^{131}I WBS is performed post therapy and also low-dose scanning for follow-up. The usual scanning dose of ^{131}I is 110-370 MBq (3-10 mCi). Patients are prepared for scanning by undertaking an iodine-free diet and withdrawal of thyroid hormone replacement for 4 weeks. Generally all patients are reviewed 1 week after ^{131}I therapy. Very few patients are lost to

follow-up. The measurement of serum thyroglobulin levels is available in the Republic of Korea at a cost of US \$10 per sample. Measurements are taken every 6-12 months, and a pre- ^{131}I therapy measurement is taken 6-8 weeks after surgery. Anti-thyroglobulin antibodies are measured with appropriate dilution techniques.

FDG PET imaging is used for patients with negative ^{131}I scans and elevated thyroglobulin levels, and where PET imaging is unavailable, whole body $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl imaging is performed under these clinical circumstances. Iodine-123 imaging is not available. Management of thyroid cancer in the Republic of Korea is perceived as being in a strong position due to the locally available ^{131}I capsules but limited by government over-regulation. There is also a perceived shortage of radioiodine therapy wards in the Republic of Korea.

Sri Lanka

The island nation of Sri Lanka has an area of 65 610 square kilometres and a population of 19.4 million. The ethnic distribution is Sinhalese 81.6%, Sri Lanka Tamil 4.4%, Indian Tamil 5.1%, Sri Lanka Moor 8%, Burgher 0.2%, Malay 0.3%, Sri Lanka Chetty 0.1%, and others 0.3%. The major religious groups include Buddhists (>75%), Muslim, Hindus and Christian [17.35]. The majority of people live in extended families. In the year 2000, the average annual per capita income was US \$876. For the year 2000, the Gross National Product of Sri Lanka was US \$16.4 billion, with a growth rate of 6%. In 1999, the percentage of total annual budget spent for health in Sri Lanka was 5.6% [17.36].

The rate of endemic iodine deficiency has been reduced following a mass salt iodination program. The incidence of thyroid cancer and its mortality in Sri Lanka is not known, as there is no established cancer registry. Thyroid cancer is approximately the fourth and fifth most prevalent cancer in females and males, respectively.

In Sri Lanka there are 36.5 physicians per 100 000 of the population. There are six medical colleges offering undergraduate medical education and four offering post-graduate medical education. Undergraduate medical training is for 5 years. Nuclear medicine is not yet a totally independent specialty and apart from informal local instruction, training in nuclear medicine is done overseas. A formal training program is available for medical physicists but nuclear medicine technology training and training in radio-pharmacy is not locally available. Currently there are four trained nuclear medicine physicians in Sri Lanka, approximately 12 nuclear medicine technologists and two nuclear medicine medical physicists. There are two government hospitals and one private hospital that provide treatment for thyroid cancer patients in Sri Lanka. Only the government hospital at the capital, Colombo, has dedicated facilities for in-patient radioiodine therapy, the other government hospital, situated 125 kilometres away, can administer only the maximum allowable single outpatient dose of ^{131}I , 1110 MBq (30 mCi) for residual ablation. The private hospital has appropriate facilities for high dose ^{131}I therapy but is costly and therefore less well utilized. The approximate bed-stay cost per day for thyroid cancer patients in Sri Lanka is US \$300. Health care in Sri Lanka is free within the government hospitals. More than 95% of thyroid cancer patients are managed within the government hospitals. The costs of the private hospital are met either by the patient or the patient's health insurance company. None of these three hospitals have their own diagnostic nuclear medicine facilities. Two other nuclear medicine units provide imaging facilities. A total of three gamma cameras and one thyroid uptake probe are available for diagnostic and post-therapy work in Sri Lanka. Radioimmunoassay kits, ^{131}I and $^{99\text{m}}\text{Tc}$ labelled radiopharmaceuticals are all imported from the United Kingdom. The Atomic Energy

Authority of Sri Lanka licenses the nuclear medicine and oncology units that use radiation for diagnostic or therapeutic purposes.

The surgeon plays a major role in the diagnosis and treatment of thyroid cancer. Patients with a suspicious lump are referred to the surgeon who may perform ^{99m}Tc thyroid scintigraphy, biochemical thyroid function tests and a fine needle aspiration biopsy. Upon histologic confirmation of thyroid cancer a near-total thyroidectomy is performed. Typically, the surgeon reassesses the patient 2-3 weeks after surgery, and where there is considered clinical evidence of metastatic disease, may commence short-term thyroxine therapy and refer the patient to a nuclear medicine unit for ^{131}I therapy. Most patients without clinical evidence of metastatic disease will receive life-long thyroxine replacement without ^{131}I therapy. Serum thyroglobulin measurement is available only through the private hospital laboratories, and is consequently considered to be expensive (US \$12-15 per sample). Those patients who can afford it will be followed by measurement every 3 months for the first year, and annually thereafter. Pre- ^{131}I therapy serum thyroglobulin levels, however, are not routinely performed. No facility is available for measurement of anti-thyroglobulin antibody levels. Those patients who have clinical metastatic thyroid cancer or elevated serum thyroglobulin levels are subsequently treated with 1.11-3.7 GBq (30-100 mCi) ^{131}I depending upon the facilities available. Endocrinologists have little involvement in the management of patients with thyroid cancer in Sri Lanka. As well as nuclear medicine physicians, radiation oncologists may also administer radioiodine to patients. Radioiodine is usually administered 6-8 weeks after surgery.

Where the facilities are available, patients may be assessed by measurement of thyroid stimulating hormone levels, serum thyroglobulin and then undergo a 48-hour low-dose (110-185 MBq or 3-5 mCi) pre-therapy ^{131}I WBS at 4-8 weeks post surgery. Those patients taking thyroxine have this ceased 4-6 weeks prior to the ^{131}I whole body scan and are advised to follow a low exogenous iodine diet. T3 is not available and considered to be prohibitively expensive. Iodine-123 is also not available in Sri Lanka. Patients are usually first followed-up 4-8 weeks after ^{131}I therapy. There is a relatively high rate of patients lost to follow-up due to geographical isolation, inadequate transport systems and general poverty. Other imaging modalities such as FDG PET imaging, and whole body imaging with ^{99m}Tc sestamibi or ^{201}Tl are not available in Sri Lanka. In addition to the fundamental lack of resources for management of thyroid cancer, there remains a lack of awareness of radioiodine therapy and nuclear medicine in general among a large proportion of the medical community in Sri Lanka.

Taiwan

The main island of Taiwan has a land area of 1100 square kilometres. There are also several other smaller islands. The population is about 24 million, and 95% of the population is of Chinese ethnicity. Cultural influences may determine patient treatment compliance with up to 30% of people preferring Chinese herb medications to prescribed medication, believing that prolonged medication is detrimental to health. The central mountainous region of Taiwan's main island has previously had rates as high as 50% of endemic iodine deficiency, but since the introduction of iodized table salt, this has fallen to around 4%.

Basic medical training in Taiwan takes 7 years and a further 3 years training is required for nuclear medicine specialty training. A radiation licence is required for practice. Taiwan has four nuclear medicine facilities that treat thyroid cancer with radioiodine. The average bed-stay cost for the isolation room, which has only single occupancy, is about US \$200. The average bed-stay cost of hospitalisation for thyroidectomy varies between US \$80-300,

depending upon how many people occupy the room. The government provides free basic health care for unemployed patients. Employed patients have National Health Insurance which is a public program co-sponsored by the government and employers.

The incidence of thyroid cancer in Taiwan (1998 Cancer Registry data) is 4/100 000 overall. For males the incidence is 1.6/100 000 and for females 6.6/100 000. The overall year 2000 mortality rate was 0.5/100 000 (0.5/100 000 for males and 0.6/100 000 for females). Most commonly, the patient is referred to an endocrinologist for diagnostic work-up of suspected thyroid cancer. This usually involves thyroid ultrasound and fine needle aspiration biopsy. When the diagnosis of thyroid cancer is established, the patient is then referred to a surgeon for near-total thyroidectomy. Following thyroidectomy the patient returns to the endocrinologist to assess the need for radioiodine therapy. If the isolation bed is available, the patient is admitted for radioiodine therapy 4 weeks after surgery. If the isolation room is not available the patient is then prescribed thyroxine until 4 weeks before the determined time for radioiodine therapy, when it is ceased. T3 is currently not available in Taiwan. rhTSH is available but its cost is not covered by insurance, and the cost of US \$1600-1800 is generally considered too expensive for most patients. The endocrinologist prescribes the ^{131}I dose, and the nuclear medicine physician administers the dose with the patient in an isolation ward.

Radioiodine is supplied as a capsule at a cost of US \$9 per 37 MBq (1 mCi). In Taiwan the legal limit of a single ^{131}I dose administered to an outpatient is 1.11 GBq (30 mCi). The usual dose range of ^{131}I for thyroid cancer is 1.11-7.4 GBq (30-200 mCi). Most commonly 4.44 GBq (120 mCi) is used. The maximum allowable radiation doses for the general public, the carer of the patient and a family infant are 5 mSv, 50 mSv and 5 mSv, respectively. The maximum post ^{131}I therapy hospital discharge dose is 8 cGy at 1 metre distance. One week after ^{131}I therapy the patient has a whole body ^{131}I scan, and the patient is followed-up in the Endocrine Clinic after an additional week. ^{131}I WBS is performed annually for the first 3 years following radioiodine therapy to monitor the patient's progress. A 185 MBq (5 mCi) scanning dose of ^{131}I is used. The patient is prepared for scanning by withdrawal of thyroxine suppression therapy for 4 weeks prior to the scan.

Serum thyroglobulin measurement is available in Taiwan at a cost of US \$6 per sample. It is measured every 3-6 months routinely during the first 3 years post radioiodine therapy. A pre- ^{131}I treatment level is also recorded four weeks after thyroidectomy. Anti-thyroglobulin antibody assay with appropriate dilutions is also available. Imaging with FDG PET is available at three sites in Taiwan. In addition, $^{99\text{m}}\text{Tc}$ sestamibi and ^{201}Tl whole body imaging are also available for patients in at least 10 hospitals. ^{123}I , however, is not available. Although Taiwan has modern facilities, currently patients may wait for up to 2 months for ^{131}I therapy due to the small number of isolation wards with appropriate facilities. Medical costs in Taiwan are increasing at a rate of nearly 10% per annum adding mounting pressure on the National Health Insurance Program.

Thailand

Thailand has a population of 62 million and covers an area of over 513 000 square kilometres. The northern and western parts of the country are mountainous, the north-eastern region consists of a large plateau and the southern and eastern regions are coastal. Endemic iodine deficiency exists mainly in the north where the prevalence of goitre was up to 80% until the introduction of iodized table salt.

There are a total of 19 nuclear medicine centres in Thailand, consisting of 16 government facilities and three privately operated facilities. Of these, 11 of the government facilities and two of the private centres offer thyroid cancer management. Each of these centres has 2-3 beds dedicated to thyroid cancer therapy. These beds may be in separate rooms or within the same room with appropriate shielding. Thailand has a total of 31 gamma cameras, 22 of which are SPECT capable. In addition there are 11 thyroid uptake probe systems. A total of 43 nuclear medicine physicians, 23 nuclear medicine technologists, 46 technicians, 12 medical physicists, 12 radio-pharmacists, 10 scientists and 30 nurses work in nuclear medicine facilities in Thailand. Basic medical training in Thailand is a six-year course. The Thai Board of nuclear medicine requires an additional three years of training for nuclear medicine specialty training. Any institution administering radioiodine therapy must obtain a licence from the Organization of Atomic Energy for Peace (OAEP), which is the radiation regulatory body in Thailand.

In Thailand, the overall incidence of thyroid cancer is 2.2/100 000. The respective incidences for males and females are 1.1/100 000 and 3.2/100 000. It is the eighth most common female cancer. A patient with a suspicious neck mass is investigated directly by fine needle aspiration biopsy (FNAB). If the FNAB is positive or suspicious, a near total thyroidectomy is the most common choice of operation performed, although sub-total thyroidectomy may be performed in provincial hospitals. If the FNAB is negative, the benign pathology is managed by follow-up observation or ethanol injection. Patients are referred to nuclear medicine physicians for radioiodine therapy following near total thyroidectomy from general surgeons or ear nose and throat surgeons. The surgeon commonly is involved in the diagnosis and management of the patient up to the time of surgery but thereafter the nuclear medicine physician manages the patient and follows the patient's progress. Endocrinologists in Thailand may also be involved in the diagnosis and evaluation of thyroid nodules, as well as management of thyroxine cancer suppression therapy of patients mainly within the private hospitals. Radiation oncologists are involved in the management of thyroid cancer patients only where external beam radiotherapy is indicated.

A National Workshop on ^{131}I Treatment of Thyroid Cancer on 16-19 Aug. 1999 at the Faculty of Medicine, Chulalongkorn University, Bangkok, established guidelines for the management of well-differentiated thyroid carcinoma. Following near-total thyroidectomy, the recommended patient preparation for radioiodine therapy includes a 4-6 week without thyroid hormone replacement and low iodine diet. T3 is available and widely used, but is three times the cost of thyroxine. rhTSH is not available in Thailand. Just prior to therapy, the patient is investigated by testing serum thyroxine, thyroid stimulating hormone, thyroglobulin and anti-thyroglobulin antibody levels. If anti-thyroglobulin antibody levels are negative, the test is only repeated every 1-2 years, whereas if positive repeat assays are performed every six months. Appropriate dilutions are applied to all measurements. Serum thyroglobulin measurement costs about US \$5 per sample. A low-dose (74-110 MBq or 2-3 mCi) ^{131}I WBS is recommended before therapy, and if this is not possible, at least a $^{99\text{m}}\text{Tc}$ thyroid scintigraphy to assess the degree of remnant thyroid tissue.

The average daily bed-stay cost for thyroid cancer treatment in Thailand is US \$20-25 for an air-conditioned room and US \$5-10 for a non-air-conditioned room in a government hospital. Within a private hospital this cost is US \$50-100. The patient is responsible for payment of this cost, although in government hospitals some patients may qualify for the social-welfare, and may pay less or even receive free treatment. In Thailand private health insurance programs may be public or privately funded, or a mixture of the two. The options include

totally private insurance, a social security program for private employees, health insurance under the Ministry of Public Health, government health care for government employees and at the patient's own expense.

The legal limit in Thailand for a single outpatient treatment dose of ^{131}I is 1.11 GBq (30 mCi). A standard ablative dose of ^{131}I is 3.7 GBq (100 mCi) or less, depending upon the amount of thyroid remnant. Where there is metastatic lymph node or lung disease 5.55 GBq (150 mCi) is used, and for bone metastases 7.4 GBq (200 mCi) is used. In Thailand the main supplier of ^{131}I is OAEP. The larger hospitals tend to use the liquid form since this is less expensive and more practical where multiple patients are treated. The cost of the liquid form is US \$0.5 per 37 MBq (1 mCi), whereas the cost for the capsule form is US \$30 for 37-740 MBq (1-20 mCi) and US \$45 for 777 MBq-1.85 GBq (21-50 mCi). A private distributor can also supply 3.7 GBq (100 mCi) capsules at a price of US \$210 each. In Thailand the maximum annual radiation dose for the general public is 5 mSv, the maximum annual radiation dose for individual carers is 20 mSv, and the maximum post ^{131}I therapy hospital discharge dose is 20 μSv /hour at one metre.

Following ^{131}I therapy, the patients have thyroxine reintroduced on the third day, with the aim of keeping the TSH levels around 0.05-0.1 $\mu\text{IU/ml}$, depending upon the patient's age, risks and presence of cardiovascular disease or osteoporosis. Patients have a post therapy ^{131}I WBS on the fifth to seventh day. Each patient is followed-up every 6 months with physical examination, low dose ^{131}I WBS, serum thyroglobulin, serum thyroxine and TSH levels. An annual chest X ray is performed. If the ^{131}I WBS is negative over the first 12 months, the scan is repeated over 3-5 years or if there is suspected recurrence based upon clinical assessment or changes in serum thyroglobulin levels. Preparation for ^{131}I WBS consists of discontinuation of thyroxine therapy and introduction of T3 for 4 weeks, before cessation of all thyroid hormone in-take for 2 weeks. Where T3 is not available thyroxine is tapered and withdrawn for 4 weeks. A TSH level $>30 \mu\text{IU/ml}$ is considered acceptable for valid interpretation of the low-dose ^{131}I WBS.

At follow-up, if serum thyroglobulin levels are rising but ^{131}I WBS is negative, anti-thyroglobulin antibody levels are again checked. In addition, whole body imaging with $^{99\text{m}}\text{Tc}$ sestamibi, $^{99\text{m}}\text{Tc}$ tetrofosmin or ^{201}Tl is performed, as well as conventional radiology techniques such as ultrasound, non-contrast CT or MRI. FDG-PET imaging is not available in Thailand. If metastatic disease is demonstrated or suspected in high-risk patients, an additional ^{131}I therapy dose is administered. Where bulky metastatic disease is demonstrated, further de-bulking surgery may be considered before additional ^{131}I therapy. If after further follow-up, there is clinical, laboratory or imaging evidence of non- ^{131}I avid disease, a re-differentiation regimen using retinoic acid A (1-1.5 mg/kg/day for 6-8 weeks) may be commenced. Where appropriate, the ^{131}I treatment dose can be repeated every 6 months as long as the cumulative dose does not exceed 37 GBq (1 Ci).

The patients who are lost to follow-up are mostly the impoverished from rural areas, particularly where the cost of transport is prohibitive. By way of example, the Chulalongkorn Hospital is the second largest hospital in Thailand and has a follow-up loss of 20% over a 10 years period, where half of these patients are lost within the first 3 years. Thailand has limited resources and consequently too few nuclear medicine facilities, particularly in peripheral localities. Furthermore, there is limited ^{131}I production by OAEP that increases costs by the use of more expensive imported ^{131}I . There is also a perceived need for further cooperation between surgeons and the nuclear medicine physicians so that all patients with well-differentiated thyroid cancer receive appropriate ^{131}I therapy.

Vietnam

Vietnam is a country of 76.2 million people. Much of Vietnam is coastal, but patches of endemic iodine-deficiency remain, particularly in the more mountainous regions. Approximately 1400 new cases of thyroid cancer are diagnosed each year. The overall incidence and prevalence of thyroid cancer are 2.0/100 000, and 3.6/100 000, respectively. Despite the cancer registry data that is now available at Ho Chi Minh City and Hanoi, data pertaining to thyroid cancer mortality has been difficult to collect. There are eight medical colleges in Vietnam but only two medical school departments of nuclear medicine (Hanoi Medical College and Ha Dong Medical College) [17.37]. In 1999 there were only two modern functioning gamma cameras in Vietnam. One of these cameras, located in Hanoi, is only available to privately insured or relatively wealthy patients. In some centres donated equipment is available. This usually consists of rectilinear scanners and thyroid uptake probes. Other basic nuclear medicine equipment such as dose calibrators is also in short supply. Radioimmunoassay testing is available for the determination of biochemical thyroid function testing. Serum thyroglobulin levels can be tested but thyroglobulin antibody levels cannot be determined.

Thyroid cancer is generally diagnosed and initially managed by the surgeon. The role of the nuclear medicine physician is principally to administer ^{131}I therapy. Radioisotopes are generally acquired from overseas sources, although some ^{131}I is available locally. Facilities are available for ^{131}I therapy of thyroid cancer complete with delay tanks for contaminated waste storage. The treatment rooms however are otherwise basic. In the Bach Mai Hospital, Hanoi a portable Geiger-Mueller radiation monitoring system is available to detect contamination in the treatment rooms. As a general rule, patients are confined to the treatment room for a minimum of 2 days post therapy. Family members often choose to stay with the patient within the treatment room.

The 60 trained nuclear medicine physicians in Vietnam have very limited resources available to them for the treatment of thyroid cancer. Limited access to modern diagnostic equipment and the inadequate local supply of ^{131}I , together with widespread poverty in the population, greatly increase the challenge for these physicians to deliver high quality health care to all that require it.

17.5. Africa

This region consists of 28 countries with populations ranging from 113.82 million to 435 000. The total population of Africa is approximately 580 million. The predominant ethnic group is indigenous Africans. Other groups those of Middle-Eastern and Asian ethnicity, and white European groups.

Algeria

This north-African country has a population of 30 million consisting of predominantly Arabic-Berber ethnicity. The climate is variable with Mediterranean conditions in the north, continental conditions centrally and dry conditions in the south. Many areas of Algeria still have a high rate of endemic iodine deficiency, despite the introduction of a national salt iodisation program in 1972.

Algeria has four nuclear medicine departments with somewhat limited resources. A total of six units have isolation wards with shielding suitable for radioiodine therapy. Thyroid cancer

represents 2% of all cancers in Algeria. The incidence is 3.2/100 000 for females and 1.2/100 000 for males. Mortality from thyroid cancer is 0.9/100 000 for females and 0.4/100 000 for males. There is a 28% recurrence rate at 10 years.

Thyroid cancer patients are predominantly referred for therapy by endocrinologists. The endocrinologist normally investigates the patient by clinical examination, thyroid scintigraphy, neck ultrasound and fine needle aspiration biopsy. Where there is a strong suspicion of thyroid cancer, chest X ray and hepatic ultrasound are also performed. Only nuclear medicine physicians provide radioiodine therapy. This is after total or near-total thyroidectomy has been performed. Nuclear medicine specialists have 7 years of undergraduate training followed by 4 year of post-graduate training. Nuclear medicine physicians are then eligible to obtain a radiation licence to treat with unsealed radiation sources.

The average hospital cost per day for thyroid cancer patients in Algeria is US \$300 but the government absorbs this cost in the free-care public hospitals. Where possible, patients are usually prepared for ^{131}I therapy 3 weeks after surgery by withdrawal of thyroxine for 4 weeks, substituted by T3, and then withdrawal of T3. Patients are also encouraged to take an iodine-poor diet. Recombinant TSH is not used in Algeria. Before ablative therapy, the patient has a low-dose ^{131}I WBS. The usual scanning dose of ^{131}I is 37-111 MBq (1-3 mCi) to avoid potential stunning. The usual dose of ^{131}I is 3.7 MBq (100 mCi) with a range of 1.1–3.7 GBq (30-100 mCi), and up to 11.1 GBq for treatment of metastatic disease. Either liquid or capsules are used for the administration of ^{131}I . The cost is US \$150 for liquid and US \$230 for a capsule. Radioiodine is purchased and supplied from an overseas company.

In Algeria the legal limit of radioiodine for an outpatient is 1.1 GBq (30 mCi). The maximum annual radiation dose for the general public is 5 mSv, for an individual carer is 50 mSv, and for a family infant is 5 mSv. Patients can be discharged from the hospital isolation ward when the patient has a dose equivalent of less than 1.1 GBq (30 mCi), or 10 micro Sv/h at one meter. The patient is reviewed by ^{131}I WBS 2-3 months post therapy. A considerable number of patients are lost to follow-up due to the small number of nuclear medicine departments, and difficulties arranging follow-up pre-scan preparations. Serum thyroglobulin is usually first measured at 1 month post thyroid ablation therapy. This test costs US \$15 per sample. Anti-thyroglobulin antibody assay is also routinely tested. FDG PET imaging is currently not available in Algeria but, if required whole body $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl imaging can be performed to assess for non-iodine avid metastases. Iodine 131 therapy of thyroid cancer has been practiced in Algeria for more than 40 years but limited resources, and only one shipment of imported ^{131}I per week restrict the number of patients that can be treated.

Ethiopia

Ethiopia has 110 hospitals serving the population of 65 million. The Tikur Anbessa Specialized Hospital is a major national referral centre for thyroid disorders. This hospital provides the only nuclear medicine service and external beam radiotherapy service in Ethiopia. The nuclear medicine department has a reconditioned gamma camera and a rectilinear camera. Currently, thyroid cancer patients are not treated in Ethiopia, and ^{131}I therapy is only available for benign thyroid diseases. Although there are no national data for the prevalence of thyroid cancer in Ethiopia, 73 patients with poorly differentiated thyroid cancer have been treated in the radiotherapy department, so that of the 2250 cancer patients referred, approximately 3% are thyroid cancer patients. It is hoped that ^{131}I therapy for thyroid cancer patients in Ethiopia will be available in the near future.

Namibia

Namibia has a population of 1.8 million, with ethnicity consisting mainly of Africans, Caucasians and mixed ethnicity. The country has deserts and vast arid regions, bushveld and swamps. Large proportions of the population reside in rural environments and have limited access to structured education. Medical training is usually in South Africa, as there is no medical school in Namibia, and takes 6 years plus 1 practical year. For specialty training in nuclear medicine additional 4 years are required. Following this a radiation licence can be obtained.

In Namibia approximately 21 cases of thyroid cancer are diagnosed each year. There are no endocrinologists in Namibia. A typical diagnostic work-up consists of clinical assessment, biochemical thyroid function tests and a ^{99m}Tc pertechnetate thyroid scan. The patient is then referred to a surgeon who performs the appropriate operation, usually near-total thyroidectomy. When pathology confirms the diagnosis, the patient is seen by a medical oncologist and dispatched to South Africa to a radiation oncology department for ^{131}I WBS and ^{131}I therapy. In situations where the patient has no private medical insurance, the state may cover the costs. In Namibia 25% of patients have private health insurance and 75% receive assistance from a public or government funded program. This consists of either self-paying patients, or where the patient has insufficient income, health care is provided for free by the government. The legal limit of a single ^{131}I dose that can be administered as an outpatient is 555 MBq (15 mCi). This is the maximum dose used to treat hyperthyroidism in Namibia, since all thyroid cancer therapy is in South Africa. Follow-up of post ^{131}I therapy patients treated for thyroid cancer is also performed in South Africa. However, occasionally ^{131}I WBS is performed using a scanning dose of 37 MBq (1 mCi). Serum thyroglobulin measurement, FDG PET imaging and ^{123}I imaging are not available in Namibia. However, ^{99m}Tc sestamibi and ^{201}Tl WBS can be performed.

A nuclear medicine department was established at Windhoek Central Hospital in 1982. A nuclear medicine physician, two technologists and a nursing sister staff the department. It is equipped with two gamma cameras. Radiopharmaceuticals are obtained from suppliers in South Africa. Compared to other countries there are limited resources available, but a close working relationship with Tygerberg Hospital in South Africa and local enthusiasm have greatly helped promote the service available to patients.

South Africa

South Africa has a population of 43.6 million. There are multiple ethnic groups within this population, the majority being African Americans (75%). The country has a geographical area of 1 219 912 square kilometres, and consists of a vast interior plateau rimmed by rugged hills and coastal plain. The incidence of thyroid cancer overall is approximately 1.0/100 000. No data on gender ratios, mortality or recurrence rates are available. The incidence of endemic iodine deficiency is unknown. Despite sophisticated large cities, poverty remains widespread in South Africa. Consequently, there may be poor compliance to medical therapy across many ethnic groups.

In South Africa there are nuclear medicine state hospital facilities that treat thyroid cancer in Cape Town, Johannesburg, Durban and Bloemfontein, and private hospital facilities in Cape Town, Johannesburg and Port Elizabeth. Nuclear medicine physicians and radiation oncologists manage ^{131}I therapy. The latter specialists also manage undifferentiated thyroid cancer or radioiodine-resistant differentiated thyroid cancer using both external beam

radiotherapy and, where appropriate, systemic chemotherapy. Medical oncologists may also be involved with such treatment. Endocrinologists have a role with the initial diagnosis of thyroid cancer, and surgeons specialising in thyroid surgery perform near-total thyroidectomy. Most patients, however are followed-up after therapy, by radiation oncologists. In order to treat patients with ^{131}I formal post-graduate qualification in either nuclear medicine or radiation oncology is required, and such physicians are required to be registered with the Atomic Energy Board and with the Health Professional Council.

In South Africa the health care system consists of both State funded hospitals and private hospitals, but privately insured patients can elect to be treated in a State Hospital. The cost for private patients in a State Hospital is US \$51 per day compared to more than US \$200 a day for private patients in a private hospital. State run health insurance costs the general public between US \$5-38 per month, depending upon income. This covers the cost of public health care in State Hospitals.

A typical diagnostic work-up of a patient with suspected thyroid cancer includes ultrasound of the thyroid and FNAB of any suspicious lesion. The histology/cytology is reviewed, and where appropriate thyroid scintigraphy is performed. The usual treatment protocol for patients with differentiated thyroid cancer following surgery includes ^{131}I therapy at 5 weeks. During this time the patient receives no thyroxine hormone replacement therapy. T3 is introduced for the first three weeks, followed by two weeks without any thyroid hormone replacement. rhTSH is not used in the State Hospitals due to its expense. ^{131}I is mainly imported from one overseas source and costs between US \$52-240 for 111 MBq (3 mCi) to 6 GBq (162 mCi). In South Africa capsules are generally used. The legal limit of a single ^{131}I dose administered to an outpatient is 370 MBq (10 mCi). In South Africa the maximum limit of annual radiation dose for the general public is 1 mSv, for individual carers 20 mSv, for family infants 1 mSv, and the maximum post ^{131}I therapy discharge dose allowed is 370 MBq (10 mCi) or 25 μSv at 1 (one) metre.

Following ^{131}I therapy and ^{131}I WBS is performed routinely, and low dose (111 MBq or 3 mCi) ^{131}I WBS is performed to monitor the patient's progress at regular intervals. In preparation for these scans the patient has thyroxine hormone replacement discontinued and T3 introduced for three weeks, before cessation of all thyroid hormone replacement therapy for two weeks. Thyroxine is re-introduced the following day if the ^{131}I WBS is negative, otherwise the patient is admitted to an isolation ward for additional ^{131}I therapy. Serum thyroglobulin measurement is only available in the private hospitals in South Africa. Data regarding the rate of patients lost to follow-up is unavailable but the most likely cause is due to economic or geographic reasons. Other imaging techniques using $^{99\text{m}}\text{Tc}$ sestamibi and ^{123}I WBS are widely available but ^{201}Tl WBS is not available and FDG-PET is not available in the State Hospitals.

Tanzania

Tanzania has a population of 35 million. The country has diverse geography and a high rate of endemic iodine deficiency goitre. Modern medical services are available, and only a few communities opt for traditional medicine as the first mode of medical care. The major barrier to medical compliance is affordability and distance to the health care facility.

The incidence of thyroid cancer in Tanzania is not known. Medical training is for five years plus a year of medical internship. In order to treat patients with radioiodine, post graduate training in nuclear medicine is required and subsequent licensing from the National Radiation

Commission. There is one nuclear medicine facility in Tanzania, which is the only centre treating thyroid cancer with ^{131}I . This centre has two gamma cameras and an isolation ward. The government offers free medical services to all cancer patients in Tanzania. However, at times of financial constraint, where the patient can afford it, chemotherapy and radioiodine cost US \$300. Most of the health care facilities in Tanzania are public, and the only specialist cancer hospital providing free care, is government run. The average cost per day of hospital stay for thyroid cancer patients is about US \$10.

Most thyroid cancer patients are referred from surgeons to medical oncologists, and then to nuclear medicine physicians for radioiodine therapy. Some patients are referred from the endocrinologist to nuclear medicine physician for further work-up, and post surgical follow-up. Radiation oncologists manage patients with advanced thyroid cancer, inoperable cases and those with widespread metastatic cancer and surgical recurrence. The typical diagnostic work-up of a patient presenting with a suspicious neck mass includes $^{99\text{m}}\text{Tc}$ thyroid scintigraphy, biochemical thyroid function testing and FNAB. Ultrasound is not routinely performed. Patients who have histology confirmed thyroid cancer generally undergo near-total thyroidectomy.

Following surgery the patients typically receive ^{131}I therapy 4-6 weeks later. This period includes a 4-5 week period of no thyroid hormone replacement. T3 is not routinely available in Tanzania because of costs. Similarly, rhTSH is not available. The legal limit of a single outpatient ^{131}I dose is 555 MBq (15 mCi). The dose administered to thyroid cancer patients is typically between 1.85-7.4 GBq (50-200 mCi). ^{131}I is currently obtained from the Atomic Energy Commission (AEC) of South Africa. Patients are discharged from the isolation ward when the dose is below 50 $\mu\text{Sv}/\text{hour}$. Due to the cost of ^{131}I , ^{131}I WBS is performed only on the fifth day after therapy. Post therapy follow-up typically occurs after 4-6 weeks. However, about 30% of patients are lost to follow-up due to geographical isolation. Serum thyroglobulin measurement is available and performed at no cost to the patient. Patients are tested at 4-6 weeks post ^{131}I therapy, at 6 months and yearly thereafter. Anti-thyroglobulin antibody measurements are not made. FDG PET imaging is currently unavailable in Tanzania, and there is no access to ^{123}I , $^{99\text{m}}\text{Tc}$ sestamibi or ^{201}Tl whole body imaging is not performed.

17.6. Latin America

This region consists of 30 countries and a total population of 508 million (year 2000 data). The population within these countries ranges from 97.5 million to 59 355 (Table 17.2). The ethnic groups consist of predominantly Hispanic groups, Indigenous Indian populations and those of African Americans ethnicity. The Latin American Thyroid Association (LATS) has been established in order to facilitate communication and education throughout Latin American countries. This association also offers management guidelines for member countries.

Bolivia

Bolivia has an overall area of 1 098 581 square kilometres. There are three main geographical regions: the highlands (about 3000 m above sea level), the subtropical region (1500-2600 m above sea level) and the tropical region (600-1500 m above sea level). Until 1986, 65% of the population had endemic iodine deficiency. Since that time a national program of iodized salt introduction has improved this rate up to 1993, but more recently surveys indicate a recurrence of the problem. The population is about 8.3 million, consisting of Quechuas (25%), Aymaras (20%), African origins, Spanish origins, Guaranies and mixed ethnic groups.

Among the Quechuas and Aymaras people there is an inherent cultural lack of the concept of chronic illness. For this reason compliance and follow-up are more difficult for the medical carers of these people. Poverty and the cost of medical care are also factors influencing patient compliance in Bolivia. The mean per capita annual income is US \$994.

No data regarding the incidence of thyroid cancer and thyroid cancer mortality is available in Bolivia. At the Instituto Nacional de Medicina Nuclear (INAMEN) in La Paz, the local experience of 1200 patients referred for investigation indicates an incidence of nine new cases during the year 2000, including eight female patients. Seven-year follow-up of 47 patients treated for thyroid cancer indicates a mortality rate of 6%. Disease recurrence following surgery and ^{131}I therapy is 12.7%.

There is only one centre in Bolivia with full nuclear medicine facilities to manage thyroid cancer. The INAMEN centre at La Paz has a modern gamma camera and an adequately shielded isolation ward is available at the San Gabriel Hospital. Another site in La Paz, as well as sites in Cochabamba, Santa Cruz, Tarija and Sucre have nuclear medicine diagnostic facilities but no facilities for in-patient ^{131}I therapy. In Bolivia, nuclear medicine physicians exclusively perform treatment of patients with radioiodine. There is currently no radiation licensing in Bolivia. Surgeons may be involved in the initial diagnostic process, perform the near-total thyroidectomy, and some surgeons also complete follow-up of their patients. In most cases, endocrinologists manage the diagnosis and follow-up of patients following surgery and ^{131}I therapy. Typically, a patient with a suspicious neck mass is investigated by $^{99\text{m}}\text{Tc}$ pertechnetate thyroid scintigraphy. FNAB is performed on those patients with a hypo-functioning nodule.

The average bed-stay cost of hospital treatment in Bolivia ranges from US \$100-800. This cost is covered by the National Insurance system but most patients have no insurance and must pay full costs. Some private insurance is also available that may cover 20-30% of costs. About 25% of the population is covered by the National Health Insurance system, 5% is covered by private health insurance and 70% has no medical insurance. ^{131}I therapy is typically undertaken 4 weeks after surgery, but if longer, patients have thyroxine hormone replacement withdrawn for 4 weeks before treatment. T3 therapy is not always available, and rhTSH is unavailable in Bolivia.

The usual dose of ^{131}I used for thyroid remnant ablation therapy ranges from 1.85-5.55 GBq (50-150 mCi) with the median dose of 3.7 GBq (100 mCi). Liquid ^{131}I is used at a cost of about US \$4 per 37 MBq (1 mCi). The main supplies of ^{131}I are imported from Argentina. In Bolivia there is no legal limit for the amount of ^{131}I that can be administered as an outpatient, and there is no legislation regarding radiation protection. The guidelines however include a maximum limit of annual radiation dose for the general public of 1 mSv, a maximum annual radiation dose for individual carers of patients of 20 mSv, and for a five year period less than 50 mSv. Seven days after ^{131}I therapy the patient has a WBS. Serum thyroglobulin monitoring is used, at a cost of US \$15 per sample, every six months without withdrawing thyroxine replacement therapy and annually with the patient withdrawn from thyroxine therapy, where there is no clinical evidence of relapse. Serum thyroglobulin levels are also checked 4 weeks after thyroid surgery, before ^{131}I therapy. Anti-thyroglobulin antibodies are tested routinely.

^{131}I WBS, using 110-185 MBq (3-5 mCi), is routinely performed 4-6 months after ^{131}I therapy, and each 6-12 months for the first two years, depending upon serum thyroglobulin levels. In preparation for the scan, the patient ceases thyroxine replacement therapy for 4 weeks. If T3 is available, the patient receives 75 μg daily for the first two weeks of this

period. A low iodine diet is also followed for 10 days before the scan. Where a patient exhibits a rising serum thyroglobulin level and a negative ^{131}I WBS, $^{99\text{m}}\text{Tc}$ sestamibi WBS is available. The cost of this scan, however, is often a limiting factor. In Bolivia, FDG-PET, ^{123}I WBS and ^{201}Tl WBS are not available.

The patient is first reviewed at four weeks post ^{131}I therapy, and at this time serum thyroxine, serum thyroglobulin and serum TSH levels are checked. Of the past 47 patients treated for well-differentiated thyroid cancer, five have been lost to follow-up. This has been attributed to social and economic reasons, as well as a lack of understanding of the condition by the patient and the patient's family. In Bolivia, there is a marked lack of uniformity in the management of thyroid cancer. Only one centre has appropriate facilities and therapy guidelines. Consequently, education of physicians and patients about the appropriate management of thyroid cancer is limited. Attempts are being made to achieve consensus in the use of ^{131}I and uniformity in a protocol to manage patients with well-differentiated thyroid cancer. Inherent problems remain due to the high cost of treatment, widespread poverty and lack of legislation and supervision from government health authorities.

Guatemala

Guatemala has a land area of 108 889 square kilometres and has borders with Mexico, Honduras, El Salvador and Belize. It has a population of 11.4 million, and at the 1995 national census the estimated annual rate of population growth was 2.8%. Indigenous Guatemalians make up 43% of the population and the remainder consists predominantly of those of mixed indigenous and European ethnicity ('Ladinos'). Up to 65% of the population resides in rural areas, and 75% live below the poverty line, 58% in extreme poverty. Of the indigenous population 32% speak only Mayan languages and 46% of the population are illiterate. These factors all influence the perception of illness and tend to increase non-compliance of medical advice and treatment. The estimated prevalence of iodine deficiency is 12% in the more remote mountainous regions and 8% in urban areas. Although no reliable data exist for thyroid cancer incidence and mortality in Guatemala, the female to male ratio is four and relapse following treatment of thyroid cancer is 10%.

There are a total of four centres in Guatemala, all located in Guatemala City that administer ^{131}I therapy. Only two of these centres have full facilities including modern gamma cameras and isolation wards. Nuclear medicine physicians as well as some endocrinologists and radiation oncologists administer ^{131}I therapy. Either the endocrinologist or the surgeon takes the key management role, supervises therapy and long term follow-up. In order to treat patients using ^{131}I , in addition to the six years of basic medical training, another three years of specialty training in nuclear medicine or radiation oncology is required. Radiation licensing is also required following completion of a course in radiation protection that is run by the Ministry of Energy and Mining of Guatemala.

A typical diagnostic work-up includes FNAB without thyroid ultrasound or thyroid scintigraphic studies. Sub-total thyroidectomy (for example, lobectomy and isthmectomy) is generally performed in patients less than 40 years of age with non-invasive (thyroid capsule intact), non-metastatic tumours less than 2 cm. This approach is most commonly employed by less experienced surgeons. Near-total thyroidectomy/total thyroidectomy is performed at major referral centres and for patients greater than 40 years of age.

The average daily bed-stay cost is US \$50 for State charity hospitals, US \$60 in social security hospitals and US \$25-65 in private hospitals depending upon the category. This cost

is covered by the State in patients in public charity hospitals and social security hospitals. The former is a free service for the impoverished, and with the latter, the patient as a private or state employee, contributes a fixed amount together with his/her employer, on a monthly basis. Up to 30% of the population has health care covered by the Social Service, 10% have private medical insurance. The remaining 60% of the population have no health care coverage.

¹³¹I therapy usually takes place four to eight weeks (on average six weeks) after thyroid surgery. Thyroxine is withdrawn for four weeks. T3 and rhTSH are not readily available in Guatemala. ¹³¹I is imported from other countries at an approximate cost of US \$10 per 37 MBq (1 mCi). It is administered in liquid form. The usual dose administered is 5.5 GBq (150 mCi). The maximum legal limit of a single ¹³¹I dose that can be administered to an outpatient is 925 MBq (25 mCi). The maximum annual radiation doses are 5 mSv for the general public, 20 mSv for individual carers and 20 mSv for family infants. The maximum post ¹³¹I therapy hospital discharge dose is 0.4 mSv/hour at one metre.

Patients are usually first followed-up at eight weeks post ¹³¹I therapy. The rate of loss to follow-up is greater than 40% of those patients treated in State hospitals, and less than 4% of private hospital patients. The high rate of follow-up loss is due to a number of factors including geographic isolation, poverty preventing good patient compliance and poor education and understanding of the disease and the need for long term follow-up. ¹³¹I WBS is not performed routinely in Guatemala due to the shortage of Nuclear medicine facilities. Those patients who do undergo ¹³¹I WBS are prepared by suspension of thyroxine replacement hormone for four weeks prior to imaging. The most usual scanning dose is 185 MBq (5 mCi). Other imaging with ^{99m}Tc sestamibi WBS is available but FDG PET, ²⁰¹Tl WBS and ¹²³I WBS are not available. Serum thyroglobulin assay has been available in Guatemala since late 2001 but only at one State hospital and two private laboratories. The test costs US \$6.50 in the State hospital and US \$15 in the private laboratories. Anti-thyroglobulin antibody assay is also routinely performed with each test. Serum thyroglobulin assay is not routinely performed before ¹³¹I therapy, and measurements are generally taken on an annual basis.

¹³¹I therapy in Guatemala is performed by fully qualified and trained personnel who follow international standards, but despite the fact that the ministry of Energy and Mines has regulation standards and controls, there is no supervision or mechanism in place to ensure compliance. Furthermore, the high cost and need for imported ¹³¹I reduces availability for treatment. The limited imaging equipment and paucity of properly equipped isolation wards reflect the unfavourable economy of Guatemala and priority directing health resources toward primary care.

Paraguay

This country of 406 752 square kilometres of land area is bordered by Argentina, Bolivia and Brazil. It has a population of 5.6 million where 95% are of the Mestee ethnic group. European white and indigenous Indian ethnic groups largely make up the remainder. There are two official languages, Spanish and the Indian language Guarani that is spoken by more than 90% of the population. Principle industries include hydroelectricity, agriculture and cattle.

In 1988 the endemic iodine deficiency prevalence was 48.6%. A Government sponsored program to reduce endemic iodine deficiency was introduced in 1991. Subsequently, the Thyromobil Project co-sponsored by the Ministry of Health, UNICEF and the ICCIDD has

found an iodine-deficiency goitre prevalence of 8.2%. In 1996/7 the median urinary iodine level was found to be 14.8 µg/dl.

Paraguay has three nuclear medicine centres that treat thyroid cancer with ^{131}I , and there are a total of seven gamma cameras (two SPECT capable) within these centres. Only three physicians specialize in the field of nuclear medicine in Paraguay, and are the only physicians to treat patients with ^{131}I . General medical training is for 6 years in Paraguay. Nuclear medicine specialty training of at least 2 years has to be obtained overseas. There is no formal radiation licensing in Paraguay. The surgeon takes the main responsibility in management of thyroid cancer patients in all aspects other than ^{131}I therapy.

The usual diagnostic approach to a patient with a suspicious thyroid mass involves $^{99\text{m}}\text{Tc}$ pertechnetate thyroid scintigraphy and thyroid ultrasound imaging. In addition, ^{131}I thyroid uptake is estimated. Under ultrasound guidance, percutaneous aspiration of the suspicious nodule is performed. Where thyroid cancer is confirmed, a near total thyroidectomy is performed but the surgical protocol may depend upon the size of the nodule, and estimated extent of disease. The average daily hospital bed-stay cost is US \$40-50. This cost is covered by the Government health care system that is funded by 9% of each employed person's monthly salary. Private health care insurance is also available but may not cover chronic illness. ^{131}I is usually given six weeks post surgery, or when the thyroid stimulating hormone (TSH) level is at least 30 µUI/ml. Serum TSH is estimated regularly over the first 2 to 4 weeks after surgery. T3 is not readily available in Paraguay, and the cost of US \$10 for 20 µg capsules is also prohibitive in most cases. rhTSH is also not readily available and prohibitively expensive.

^{131}I is usually used in the liquid form. This is imported from an overseas source at a cost of US \$230 for 3.7 GBq (100 mCi). The usual dose given for thyroid remnant ablation is 3.7 GBq (100 mCi), and for metastatic disease 5.5-6.5 GBq (150-175 mCi). In Paraguay the legal limit of a single ^{131}I dose for an outpatient is less than 1.11 GBq (30 mCi). The maximum annual radiation dose allowed for the general public is 1 mSv and the maximum annual radiation dose for individual carers is 20 mSv or 100 mSv over 5 years.

The patient is usually discharged home from the isolation ward 48-72 hours after ^{131}I therapy. The ^{131}I WBS is done at this time, and thyroxine hormone replacement is commenced. Every six months the patient is evaluated by measurement of serum thyroglobulin, thyroid function testing and ^{131}I WBS. Serum thyroglobulin measurement costs about US \$15-20 per sample. Measurement is also made about one to two weeks prior to ^{131}I therapy. Five or six different laboratories in Paraguay assay anti-thyroglobulin antibody levels and also use appropriate dilutions. ^{131}I WBS is performed using 185-370 MBq (5-10 mCi) doses of ^{131}I . Patients are prepared for imaging by cessation of thyroxine hormone replacement for two to four weeks, and TSH to reach at least 30 µUI/ml. For those patients with increasing serum thyroglobulin levels and negative ^{131}I WBS, whole body imaging with Tc-99 sestamibi or ^{201}Tl is available but restricted due to high cost. ^{123}I WBS is not used in Paraguay and FDG-PET imaging is not available.

There is usually good patient compliance with the first follow-up visit at six months, but the loss to follow-up is high after this time. Economic and geographic reasons account for most loss to follow-up. The importation of ^{131}I means that 15-20 days notice is required before a therapy dose of ^{131}I can be delivered. This means that patient scheduling for therapy and ^{131}I WBS is made very difficult, and no urgent supply is available. Furthermore, all imported ^{131}I and other radiopharmaceuticals have to go through the standard administrative process at

customs, also adding to the delay in obtaining these products at the airport. In Paraguay there is no government support or private organizations offering support for nuclear medicine. Consequently, dissemination of knowledge to medical students and medical practitioners throughout Paraguay is very difficult, and nuclear medicine is greatly under-utilized. With only three practicing nuclear medicine physicians, limited equipment and no government support, the speciality of nuclear medicine in Paraguay is unlikely to keep pace with other countries.

17.7. Conclusions

The management of thyroid cancer is undertaken in a relatively standardized fashion throughout the world. This has been based largely upon standards and regulations set as benchmarks from North America and Europe, where resources are most available for research and data collection. Even countries with very few resources have a basic infrastructure in place that allows physicians to follow the recommended management protocols. The profound lack of resources in some countries however, prevents optimal basic diagnosis and limited follow-up (Tables 17.2, 17.3). Furthermore, lack of resources limits the number of sites where thyroid cancer therapy can be undertaken. This may prohibit therapy in some cases, and result in increased costs of transport and overnight accommodation for patients who cannot afford such expense.

Thyroid carcinoma is a disease that requires diligent long term, and often lifelong follow-up surveillance. Poverty, poor transport infrastructure and geographic isolation all contribute to inadequate long term management of patients with thyroid cancer in many developing countries. Continuing education of physicians is required in order to instigate appropriate management algorithms. In turn, the physicians need to promote education of the general public and dispel misinformation, so that patients will seek appropriate medical help as early as possible. In many countries cultural factors may also inhibit appropriate management of thyroid cancer. Patients may seek traditional family therapies as alternatives to modern medicine, and due to lack of information, may fear modern medical equipment and techniques. In addition to patient and physician education, there exists a need for the establishment of data registries in many countries. Even with the introduction of new equipment and staff, unless data is collected that accurately reflects the impact, or otherwise, of any change, the true benefit of change cannot be assessed. Such data is also a powerful tool for use at administrative and government levels in order to argue the benefit for ongoing financial support, or the need for additional support.

This review of the experience related from various countries around the world offers insight as to the effectiveness of information networks related to the availability of information technology, and groups and societies whose goals are for the optimal management of as many patients as possible. It would appear that much remains to be done in order to achieve these goals. However, this review indicates that there is much potential for improvement, and also that an inertia of knowledge growth has developed that should provide us with optimism for the future.

TABLE 17.2. COMPARISON OF SOME ASIA-PACIFIC, AFRICAN AND LATIN AMERICAN COUNTRIES

Country	Population (millions)	Thyroid Cancer Incidence (per 100 000)		Endemic Goitre (>10%)	GNP/head population (as per OECD ^a)
		Males	Females		
Algeria	30	1.2	3.2	Yes	C
Australia	18.7	2.9	8.9	No	A
Bangladesh	123.8	-	-	Yes	E
Bolivia	8.3	-	-	Yes	C
China	1259	1.2	2.9	Yes	D
Ethiopia	65.3	-	-	-	E
Guatemala	11.4	-	-	Yes	C
India	1000	0.7	2.1	Yes	D
Iran	65	-	7.7	No	C
Japan	127	1.9	8.7	No	A
Namibia	1.8	-	-	Yes	C
Pakistan	130.6	-	-	Yes	D
Paraguay	5.6	-	-	No	C
Philippines	76.5	2.6	7.9	Yes	C
South Africa	43.6	-	1.0	-	C
South Korea	45	1.5	8.1	No	B
Sri Lanka	19.4	-	-	No	C
Taiwan	24	1.6	6.6	No	B
Tanzania	35	-	-	Yes	E
Thailand	62	1.1	3.2	Yes	C
Vietnam	76.2	-	2.0	Yes	D

^a OECD (Organization for Economic Cooperation and Development) classification based on aid recipients at January 2001: A developed country, B more advanced country in transition to developed, C developing country with low-middle income per capita GNP (US \$761-3030 in 1998), D developing country with low income per capita GNP (US \$ < 760 in 1998), E least developed country.

TABLE 17.3. COMPARISON OF AVAILABLE RESOURCES FOR MANAGEMENT OF THYROID CANCER

Country	Isolation Wards	¹³¹ I	Tg Assay	Gamma Cameras	FDG PET Imaging	¹²³ I Imaging	^{99m} Tc Sestamibi/ ²⁰¹ Tl WBS
Algeria	B	B	B	B	A	A	B
Australia	C	C	C	C	B	B	C
Bangladesh	B	B	B	B	A	A	B
Bolivia	B	A	B	B	A	A	B
China	B	C	B	B	B	B	B
Ethiopia	A	A	A	B	A	A	A
Guatemala	B	A	B	B	A	A	B
India	B	B	B	B	B	A	B
Iran	B	C	C	B	A	A	B
Japan	C	C	C	C	C	C	C
Namibia	B	A	A	B	A	A	B
Pakistan	B	C	B	B	A	A	B
Paraguay	B	A	B	B	A	A	B
Philippines	B	B	B	B	B	A	B
South Africa	B	B	C	B	B	C	C
South Korea	B	C	C	C	B	A	B
Sri Lanka	B	A	B	B	A	A	A
Taiwan	B	C	C	C	B	A	B
Tanzania	B	A	B	B	A	A	A
Thailand	B	B	C	B	A	A	B
Vietnam	B	B	B	B	A	A	A

- No data available.
A Unavailable locally.
B Limited to large centres.
C Widely available.

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18. MOLECULAR GENETICS

Carcinogenic process is considered to be a series of events induced by genetic, epigenetic and environmental factors, which alter normal cell growth. These factors may be considered as 'initiators' and 'promoters'. Initiators include agents such as chemicals and radiation which initially damage DNA itself and can induce tumours. Promoters are agents such as TSH, which radically increase tumour development. In human beings X ray treatment is the sole known initiator, and other than elevated TSH, no promoters are clarified. The long term follow-up studies of external radiation-exposed victims of Hiroshima and Nagasaki have indicated the elevated risk of thyroid cancer during the lifespan of exposed individuals. Furthermore, the dramatic increase of childhood thyroid cancer around Chernobyl has changed conventional concept and understandings of the mechanism of radiation-induced thyroid carcinogenesis. The genes subject to mutations in thyroid carcinogenesis can be classified as oncogenes or anti-oncogenes (tumour suppressor genes) based on their mode of action. Some genetic changes leading to thyroid cancer are inherited through the germline, but most are acquired or somatic in nature. Here the molecular genetics of human thyroid cancer is summarized from the standpoint of genetic factors and environmental status. Especially discussed is the molecular mechanism of radiation-induced thyroid carcinogenesis.

18.1. Oncogenes

According to the accomplishment of 'Human Genome Project', numerous 'oncogenes' have been recognized [18.1-18.2], and commercial molecular diagnostics is expected to be soon established at the clinical laboratory [18.3]. These genes, normally silent, can become activated by chromosomal translocations, deletions, or mutations, and then can 'transform' normal cells into a condition of uncontrolled growth. Most oncogenes appear to be closely related to normal growth factors, genes that control cell division or to hormone receptors [18.4-18.5]. In general, these genes, when turned on, promote cell growth, division and depress differentiation. Typically, activation of one such gene may not be enough to produce malignancy, but if accompanied by the expression of another oncogene, or if gene mutation or reduplication occurs, the cell may progress towards the transformation. Thus, sequential and accumulated DNA damages occur during cancer development. The escape mechanism from cell apoptosis is also critical for abnormal cell proliferation. The genetic and chromosomal instability subsequently also occurs during the development of thyroid cancer. Expression of c-myc is stimulated in normal thyroid cells by TSH, and overexpressed in adenomas and carcinomas in humans. Recently mutations of thyroid hormone receptors have been reported in human thyroid cancer tissues, suggesting the up-regulation mechanism of c-myc at the transcriptional level [18.6]. Activating mutations of H-ras at codons 12, 13, and 61 and overexpression of H-ras, are found in adenomas and carcinomas, but H-ras mutations are also found in nodular goitre tissue, suggesting that H-ras mutations could be an early event in oncogenesis [18.7]. Other studies, however, find ras mutations uncommon [18.8]. Enhanced sensitivity to apoptosis in ras-transformed thyroid cells may suggest the complexity of intracellular signal transduction during the early stage of thyroid oncogenesis [18.9].

Another important oncogene is frequently and specifically expressed in papillary thyroid cancers. The proto-oncogene is found on chromosome 10 (same area of the MEN type II gene as well) [18.10], and its activation involves inter- or intrachromosomal rearrangement of the tyrosine kinase domain of the ret gene so that it is attached to different promoters, producing different types of ret/PTC [18.11]. This rearrangement leads to constitutive expression of the oncogene and intra-thyroidal expression of ret/PTC can really induce papillary thyroid cancer

as confirmed by transgenic animal models [18.12, 18.13]. Recently a mutational change has been associated with follicular thyroid cancers. In 5 of 8 follicular cancers, Kroll, et al. found translocation of the DNA binding domain of PAX8 to domains A-F of the peroxisome proliferator-activator receptor (PPAR) γ 1 gene [18.14]. However, we could not prove and follow these findings in follicular cancers. Other types of gene rearrangements are rare in human thyroid cancers.

Mutations in the proteins involved in the normal TSH-receptor-G protein-adenylate-cyclase-kinase signal transduction pathway also play a role in tumour formation and development. Activating TSH receptor mutations have been found to be the cause of most hyperfunctional nodules, and are now known to be common in 'hot' nodules in patients with multi-nodular goiter [18.15, 18.16]. These mutations affect extracellular loops of the transmembrane domain and the transmembrane segments, and are proven to induce hyperfunction by transfection studies. Mutations of the stimulatory GTP binding protein subunit are also present in some patients with hyperfunctioning thyroid adenomas. TSH receptor mutations are, however, unusual in thyroid cancer [18.17]. TSH receptor expression tends to be lost as cancers de-differentiate, and persistence of its expression may be associated with a better prognosis.

18.2. Anti-oncogenes

Compared to oncogene activation, second mechanism of thyroid carcinogenesis arises from inactivating mutations in genes that normally serve to limit cell proliferation. Such genes are termed antioncogenes (tumour suppressor genes). Critical cell cycle regulation is coordinated by various types of genes such as retinoblastoma protein, pRb and p53, DNA damage repairing enzymes (hMSH2), and cell adhesion molecules (APC, DCC) [18.18, 18.19]. In general, single functional copy of antioncogene is sufficient to provide normal physiologic effects. pRb genes are normally present in both sets (maternal and paternal) of chromosomes. In retinoblastoma the inherited lack of one suppressor (pRB) gene does not cause disease, but if a genetic event (deletion, recombination, mutation, etc.) that causes failure of expression of the second allele, various types of cancer may ensue. The occurrence of tumour-specific suppressor genes is often detected by the lack of heterozygosity of chromosomal markers associated with deletions of segments of genetic material. Thus, evidence for characteristic chromosomal abnormalities within tumour cells may lead to recognition of a tumour suppressor gene. Deletion of the tumour suppressor genes, p53 and pRB, have been detected in differentiated and undifferentiated thyroid cancers. Mutation or deletion of the p53 tumour suppressor gene is found in only few differentiated thyroid cancers, but in many undifferentiated cancers, suggesting that this genetic deletion may be one of the final steps leading to anaplastic thyroid cancer growth [18.20]. Recently another tumour suppressor gene, p16^{INK4a}, has been focused on in both papillary and follicular thyroid cancers [18.21-18.22]. p16^{INK4a} encodes an inhibitor of key component of the cell cycle machinery, cyclin kinases CDK 4 and 6. p16 inactivation has been observed ranging from large-scale deletion of the locus through point mutation to promoter methylation in ~30% of well-differentiated thyroid cancers. The involvement of cell cycle regulators remains to be further clarified at the standpoint of tumour suppressor gene during thyroid oncogenesis.

18.3. Genetic background of radiation-induced tumorigenesis

The genetic background of an individual can influence the susceptibility to carcinogenesis. Germ line mutations in antioncogenes such as p53 or pRb may result in an increased prevalence of both spontaneous and induced tumours. Age of an individual at the time of exposure to imitators such as radiation is also very critical. According to the microsatellite

instability studies [18.23], early and fast-growing aggressive post-Chernobyl thyroid cancers are characterized by an increase of microsatellite instability. Hot spot areas of microsatellite instability in thyroid cancer may imply clinicopathological and prognostic significance [18.24]. Interestingly, radiation-induced thyroid cancer is all papillary type in its histological diagnosis. Although papillary thyroid cancer is heterogeneous, the global expression pattern of mRNA by cDNA microarray showed remarkable consistency [18.25]. If it could be identified the reproducible and specific molecular changes by cDNA microarray, clue of radiation-induced thyroid cancer may be obtained. However, this remains to be further clarified. Although precise genomic data how does a single nucleotide polymorphism of these antioncogenes influence thyroid carcinogenesis, familiar non-medullary thyroid cancer may give another hint to elucidate the genotype and phenotype relationship of human thyroid cancers.

The genetic background of DNA repair and mutagenesis is also an important field to provide the molecular basis of thyroid carcinogenesis. Individual variation in response to radiation and other environmental carcinogenic factors will be surely solved in the near future according to the completion of 'Human Genome Project'.

18.4. Familial thyroid tumourigenesis

Familiar thyroid cancer can arise from parafollicular cells (familiar medullary thyroid cancer) (Table 18.1) or from follicular cells (familiar non-medullary thyroid cancer) [18.26]. Medullary thyroid cancers usually occur as part of several familial syndromes, which may involve heritable loss of tumour suppressor genes. Papillary thyroid cancer occurs rarely as an independent familial syndrome, but more commonly thyroid tumours arise as part of more complex heritable diseases. Thyroid cancer also co-occurs in patients with familial adenomatous polyposis of the colon (APC) and can occur in the absence of bi-allelic inactivation of the APC gene [18.27-18.28]. Differentiated thyroid cancer is reported to co-occur with chemodactomas of the carotid body, which can be inherited in a familial autosomal dominant form. Cowden's disease is a familial syndrome which includes a variety of hamartomas, multinodular goiter, and cancers of several tissues including breast, colon, lung, and thyroid, especially in women [18.29]. Thyroid cancer is also associated with Gardner's syndrome. Another rare syndrome is Carney complex, which is inherited as an autosomal dominant trait and may simultaneously involve multiple endocrine neoplasia [18.30]. Therefore, thyroid cancer is associated with Carney complex. Family study of Carney complex strongly suggests the involvement of tumour suppressor gene, R1 α subunit of c-AMP dependent protein kinase A, located on 17q22~24 [18.31]. There are case reports describing the association of thyroid cancer in patients with Peutz-Jaghars syndrome [18.31-18.33] and ataxia-teleangiectasia. Papillary thyroid carcinoma has been associated with papillary renal neoplasia in a distinct heritable tumour syndrome.

18.5. Molecular mechanism of radiation-induced chromosomal damages

Before understanding thyroid carcinogenesis, it is essential to clarify the molecular genetics of interaction between genotoxic potential of environmental factors such as irradiation and DNA damages, which increase cancer risks in humans [18.34]. Irradiation generates free radicals and reactive oxygen species such as superoxide, peroxide, hydroxyl radicals and their intermediates, which in turn induce lipid peroxidation of membranes and cell structures. Indeed, it has already been demonstrated a unique pattern of released ceramide and diacylglycerol in response to irradiation in cultured human thyroid cells [18.35]. A certain

degree of imbalance upon the oxidative stress may occur between radical-generating and radical-scavenging systems, leading to DNA damages including chromosomal and cellular alterations [18.36]. Human thyroid cells are obviously radioresistant and prone to survival, rather than to apoptosis through specific intracellular signal transduction systems [18.35, 18.37-18.39]. Another important finding is that increased production of superoxide radicals may induce the release of chromosome-damaging factor, the clastogenic factors in circulating plasma [18.40]. These low-molecular weight substrates produced via superoxide may induce further production of reactive radicals, perpetuate and eventually enhance DNA damages. Therefore, special attention on the role of indirect as well as direct mechanisms in determining the final and complex effect of ionizing radiation on thyroid carcinogenesis.

TABLE 18.1. FAMILIAR SYNDROMES COMPLICATED WITH HEREDITABLE NON-MEDULLARY THYROID CANCERS

Syndrome	Clinical Presentation	Thyroid Pathology	Gene and Location
Familial Papillary Carcinoma	-	Papillary cancer	Unknown
Familial Polyposis	Large intestine polyps and other GI tumours	Papillary cancer	APC on 5q21
Gardner's Syndrome	Small and large intestine polyps, osteomas, fibromas, lipomas	Papillary cancer	APC on 5q21
Turcot's Syndrome	Large intestine polyps Brain tumours	Papillary cancer	APC on 5q21
Cowden's Disease	Multiple haematomas and breast tumours	Follicular adenoma and cancer	Unknown
Carney Complex	Pigmented adrenal nodules, pituitary adenomas, spotty skin pigmentation, myxomas	Thyroid adenomas	PKARIA on 17q22~24, and another gene

18.6. Radiation-induced thyroid carcinogenesis

In this discussion it should be noted that the carcinogenic effects of irradiation and excess TSH secretion, and other related thyroid tumour initiators or promoters.

Mechanisms by which radiation causes thyroid changes are not certain, but there is a strong evidence of primarily TSH dependent thyroid carcinogenesis in animal models. Either external or internal irradiation such as radioactive iodine may act on thyroid gland as an initiator of hyperplasia through the TSH stimulation. However, radiation can directly cause genetic alterations in chromosomes, followed by the appearance of errors in DNA replication and escape from apoptosis of a cell which finally may develop thyroid cancer [18.41-18.43].

Understanding the specificity of RET mutations associated with various tumour diseases has fundamental clinical relevance [18.44]. Genetic screening for ret mutations is originally a powerful diagnostic tool for the unambiguous diagnosis of multiple endocrine neoplasia (MEN) type II gene carriers, which allows presymptomatic thyroidectomy at an early stage of the disease [18.45]. Similarly, the identification of ret/PTC rearrangement may be of help in the differential diagnosis of thyroid tumoural diseases, in particular for distinguishing between highly aggressive anaplastic thyroid tumours (which are negative for this rearrangement) and papillary cancer [18.46].

RET encodes a tyrosine kinase (TK) receptor for growth factors of the glial cell line derived neurotrophic factor (GDNF) family [18.47] (Fig. 18.1). GDNF family comprises TGF- β -related molecules, including mainly GDNF and neurturin (NTN), which have trophic effects on a variety of neuronal populations. They mediate their action through multicomponent receptor systems composed of a ligand-binding glycosyl-phosphatidylinositol (GPI)-linked protein (designated GFR α) and the RET kinase. Two GPI-linked proteins have been initially isolated: GFR α 1 or GFR α 2, GDNF is the preferred ligand for GFR α 1 while NTN binds preferentially GFR α 2. Recently, a novel GDNF-related neurotrophic factor, designated persephin (PSP), and a novel GFR α -like receptor, GFR α 3, have been isolated, but it is still unclear whether they are able to stimulate RET. RET mutations cause several different types of human diseases such as MEN types 2A and 2B, papillary thyroid cancer and Hirschsprung's disease. The mutations of Hirschsprung's disease cause a 'loss-of-function' of RET mediated by different molecular mechanisms [18.48].

Besides of RET mutations observed in MEN types 2A and 2B, and Hirschsprung's disease, specific rearrangements of RET have been found only in human thyroid cancer of the papillary subtype [18.49]. These rearrangements lead to the fusion of the RET TK domain to the 5'-terminal regions of heterologous genes, generating chimeric oncogenes designated ret/PTC. RET fusion partners are the H4, RI, RFG (ELE1), and RFG5 genes in the case of ret/PTC1, 2, 3 and 5, respectively (Fig. 18.2). There are more than eleven types of ret/PTC rearrangements. The fusion between RFG and RET genes usually lacks the transmembrane domain of RET. By substituting RET transcriptional promoter with those of the fusion partners, these rearrangements drive the expression of RET in the thyroid gland; moreover, the fusion partners contain coiled-coil domains which cause a constitutive dimerization and kinase activation of the rearranged RET products (Fig. 18.3). Such constitutive active forms of ret/PTCs are closely involved into and eventually result in thyroid carcinogenesis [18.50]. The exact molecular mechanism of ret/PTC formation in thyroid cells remains to be further clarified but recently chromosomal recombination has been demonstrated by in situ hybridization study in radiation-induced thyroid papillary cancer [18.51]. Indeed, ret/PTC oncogenes are present in about 40% of human papillary carcinomas and are absent in other tumoural subtypes [18.52, 18.53]. Although the ret/PTC rearrangements are commonly observed in sporadic papillary thyroid cancers of children and young adults [18.54], high prevalence of these rearrangements is detected around Chernobyl as well as in the population exposed to external radiation [18.55].

A dramatic increase in the incidence of papillary thyroid cancer has been reported in Belarus and Ukraine following the Chernobyl nuclear accident on April 26, 1986 which strongly suggests the involvement of ret/PTC in the aetiology of childhood thyroid cancers [18.56-18.57]. ret/PTC rearrangements, mainly of the ret/PTC3 type, have been reported to occur with high frequency in these Chernobyl-associated childhood papillary cancers [18.58]. It is conceivable that ionizing radiation promotes the formation of RET alterations after a double-

strand break of genomic DNA has taken place. Since *ret*/PTC rearrangement has been examined in spontaneous or radiation-induced papillary thyroid cancers in the world, the summary of reports is demonstrated in Table 18.2. The positive ratio of *ret*/PTC rearrangement exhibits a significantly higher prevalence in radiation-induced thyroid cancers than in spontaneous papillary thyroid cancers. In 59 papillary thyroid cancers from children (21 males and 38 females) living in Belarus at the time of the Chernobyl reactor accident, 36 showed *ret*/PTC rearrangement. *ret*/PTC3 is the most prominent type and almost 64% of all RET rearrangement-positive tumours revealed this form of rearrangement. *ret*/PTC2 is not found at all. *ret*/PTC1, the prevailing type in adult papillary thyroid cancers, is observed in only eight tumours. ELE1/RET or H4/RET rearrangements are most likely due to radiation-induced double strand breaks with subsequent illegitimate recombination. Recently, Rabes, et al. investigated molecular genetic aberrations in 191 papillary thyroid cancers from patients exposed at young age to radioiodine released from the Chernobyl reactor [18.49]. The results show most RET rearrangement forms are *ret*/PTC1 and *ret*/PTC3 (Table 18.2). When the tumours developed during the first decade after the accident were compared with those that occurred later, a significantly higher prevalence of rearrangement-positive tumours was found in faster developing papillary thyroid cancers (Table 18.3). Among *ret*/PTC rearrangement-positive papillary cancers, tumours exhibiting ELE1/RET showed the fastest development. Sixty-three per cent of the tumours exhibiting an ELE1/RET rearrangement were found up to 10 years after exposure, in contrast to H4/*ret* tumours, which are present in a low percentage at short latency periods but in 81% at a latency of >10 years ($P < 0.001$). Based on these data, the early high prevalence of ELE1/RET rearrangements decreases with time after the accident. At a latency longer than 10 years, the H4/RET becomes the predominant molecular alternation. The results also show that the age at radiation exposure lacks relation to a specific type of gene rearrangement (Table 18.4). The age group from 0 to 4 years at the time of irradiation included slightly more rearrangement-positive tumours than negative tumours. This difference was not statistically significant ($P = 0.7$) when compared with the age group >4~8 years (Table 18.5) or when compared with the total age group older than 4 years. In the age group 0~4 years, tumours of the ELE1/RET type are slightly less frequent than H4/RET tumours. Their number is identical in the age group >4~8 years. Patients older than 8 years at irradiation exhibit more PTC1 than PTC3, but a statistically significant difference between the prevalence of H4/RET and ELE1/RET was not observed in any age group. These results argue against the hypothesis that ELE1/*ret* is the preferred type of rearrangement after irradiation at young age.

Having found several rare *ret*-fused partners in RET activation among childhood papillary thyroid cancers after Chernobyl, it might be predicted that high probability of radiation-induced double strand breaks in the thyroid of the exposed population will give rise to the discovery of even more new rare gene fusion products in these tumours in the future.

Ectopic self-dimerization mediated constitutive activation of an intracytoplasmic RET tyrosin kinase with putatively altered substrate specificity appears to be an essential prerequisite of radiation-induced papillary thyroid cancers in children after Chernobyl accident. In addition to radiation, young age at exposure could also be a critical determinant for the preference of ELE/RET rearrangements. However, at the present time, definite conclusions about the role of several parameters (e.g., accurate dose of irradiation, age, physiological stage of the thyroid gland, or hyperplastic processes after radiation-induced cell loss) in the induction and progression of thyroid carcinomas in children after Chernobyl are difficult to draw. Besides of the reports of radiation-associated *ret*/PTC gene rearrangement, papillary thyroid microcarcinomas (measuring 1 cm or less in diameter) possess high frequency of *ret*/PTC rearrangements, suggesting that constitutive active form of RET gene plays a role in the

initiation of thyroid tumourigenesis but does not seem to be necessary for further progression of the tumour [18.59].

In summary, the activation of RET gene contributes to the development of human cancers in two different ways [18.60]. First, germ-line mutations, mainly point mutations, lead to constitutive activation of RET tyrosine kinase activity in parafollicular cells. Second, somatic rearrangements of RET with a variety of activating genes contribute to unscheduled expression and constitutive dimerization of chimeric ret/PTC genes in thyroid follicular cells. ret/PTC rearrangement seems to be significantly more frequent in tumours in irradiated younger patients than in spontaneous thyroid cancers.

TABLE 18.2. RET/PTC REARRANGEMENTS IN SPONTANEOUS AND RADIATION-INDUCED PAPILLARY THYROID CANCERS

Country	Spontaneous		Total (n)	Radiation-induced		Total (n)	Reference
	N	%		n	%		
Canada	3	5	60	-	-	-	Sugg, et al. (1996) [18.64]
France	8	11	70	-	-	-	Santoro, et al. (1992) [18.65]
France	2	10	19	-	-	-	Said, et al. (1994) [18.66]
United Kingdom	2	6	30	-	-	-	Wynford-Thomas, et al. (1993) [18.67]
Italy	14	33	42	-	-	-	Santoro, et al. (1994) [18.68]
Italy	18	35	52	-	-	-	Bongarzzone et al. (1994) [18.69]
Japan	1	9	9	-	-	-	Ishizaka, et al. (1991) [18.70]
Japan	1	3	38	-	-	-	Wajjwalku, et al. (1992) [18.71]
Saudi Arabia	1	3	40	-	-	-	Zou, et al. (1994) [18.72]
USA	4	11	36	-	-	-	Jhiang, et al. (1992) [18.73]
USA	11	17	65	-	-	-	Santoro, et al. (1992) [18.74]
USA	11	65	17	-	-	-	Nikiforov, et al. (1997) [18.75]
Belarus	-	-	-	4	56	7	Ito, et al. (1994) [18.76]
Belarus	-	-	-	36	61	59	Klugbauer, et al. (1995, 1996) [18.77, 18.78]
Belarus	-	-	-	4	66	6	Fugazzola, et al. (1995) [18.79]
Belarus	-	-	-	29	76	38	Nikiforov, et al. (1999) [18.80]
France	3	15	20	16	84	19	Bounacer, et al. (1997) [18.81]
Total	79	15.8	500	89	69.0	129	

TABLE 18.3. RET AND NTRKI REARRANGEMENT IN PAPILLARY THYROID CANCER OF CHILDREN FROM BELARUS THYROIDECTOMIZED IN MINSK DURING THE FIRST DECADE AFTER THE CHERNOBYL REACTOR ACCIDENT (n = 61)

Type of rearrangement	n	% of total	% of rear. — pos. tumours	% of RET rear. — pos. tumours
No rearrangement	21	34.4		
RET and NTRKI rearrangement	40	(65.6)	(100)	
RET rearrangements	38	62.3	95.0	(100)
PTC 1 (H4/RET)	9	14.8	22.5	23.7
PTC 2 (R1 α /RET)	0	0	0	0
PTC 3 (ELE/RET)	24	39.3	60.0	63.2
PTC 5 (GOLGA5/RET)	1	1.6	2.5	2.6
PTC 6 (HTIF/RET)	1	1.6	2.5	2.6
PTC 7 (RGF7/RET)	1	1.6	2.5	2.6
PTC X (X/RET)	2	3.3	5.0	5.3
NTRKI rearrangements	2	3.3	5.0	
TPM3/NTRKI	1	1.6	2.5	
TPK-T2	1	1.6	2.5	

TABLE 18.4. CHANGES IN THE PREVALENCE AND TYPE OF RET AND NTR1 REARRANGEMENTS IN 191 PAPILLARY THYROID CANCERS OF CHILDREN AFTER THE CHERNOBYL REACTOR ACCIDENT ON 26 APR. 1986, AS A FUNCTION OF THE TUMOUR LATENCY PERIOD (INTERVAL BETWEEN EXPOSURE AND DIAGNOSIS/THYROIDECTOMY)

Latency period	Total	Rearrangement positive		Rearrangement negative		PTC 1		PTC 3		PTC 5, 6, 7, X		NTRK1	
		n	%	n	%	n	% ^a	n	% ^a	n	% ^a	n	% ^a
		Total (7-11.7 years)	191	100	52.4	91	47.6	48	48.0	38	38.0	8	8.0
<10 years	61	40 ^b	65.6	21 ^b	34.4	9 ^c	22.5	24 ^c	60.0	5	12.5	2	5.0
>10 years	130	60 ^b	46.2	70 ^b	53.8	39 ^c	65.0	14 ^c	23.3	3	5.0	4	6.7

^a Percentages from total number of rearrangement-positive PTCs in this latency group.

^b P < 0.012.

^c P < 0.001.

TABLE 18.5. PREVALENCE AND TYPE OF RET AND NRK1 REARRANGEMENTS AS A FUNCTION OF AGE AT RADIATION EXPOSURE (n= 191)

Age at radiation exposure (year-old)	Total number	Rearrangement positive		Rearrangement negative		PTC 1		PTC 3		PTC 5, 6, 7, X		NTRK1	
		n	%	n	%	n	% ^a	n	% ^a	n	% ^a	n	% ^a
		<4	108	61 ^b	56.5	47 ^b	43.5	28 ^c	45.9	25 ^c	41.0	4	6.6
>4 ~ 8	41	18	43.9	23	56.1	7	38.9	7	38.9	2	11.1	2	11.1
>8 ~ 12	18	9	50.0	9	50.0	5		3		1		0	
>12 ~ 16	14	7	50.0	7	50.0	5		2		0		0	
>16	10	5	50.0	5	50.0	3		1		1		0	
>4	83	39 ^b	47.0	45 ^b	53.0	20 ^c	51.3	13 ^c	33.3	4	10.3	2	5.1

^a Percentages from total number of rearrangement-positive PTCs in this age group.

^b P > 0.7.

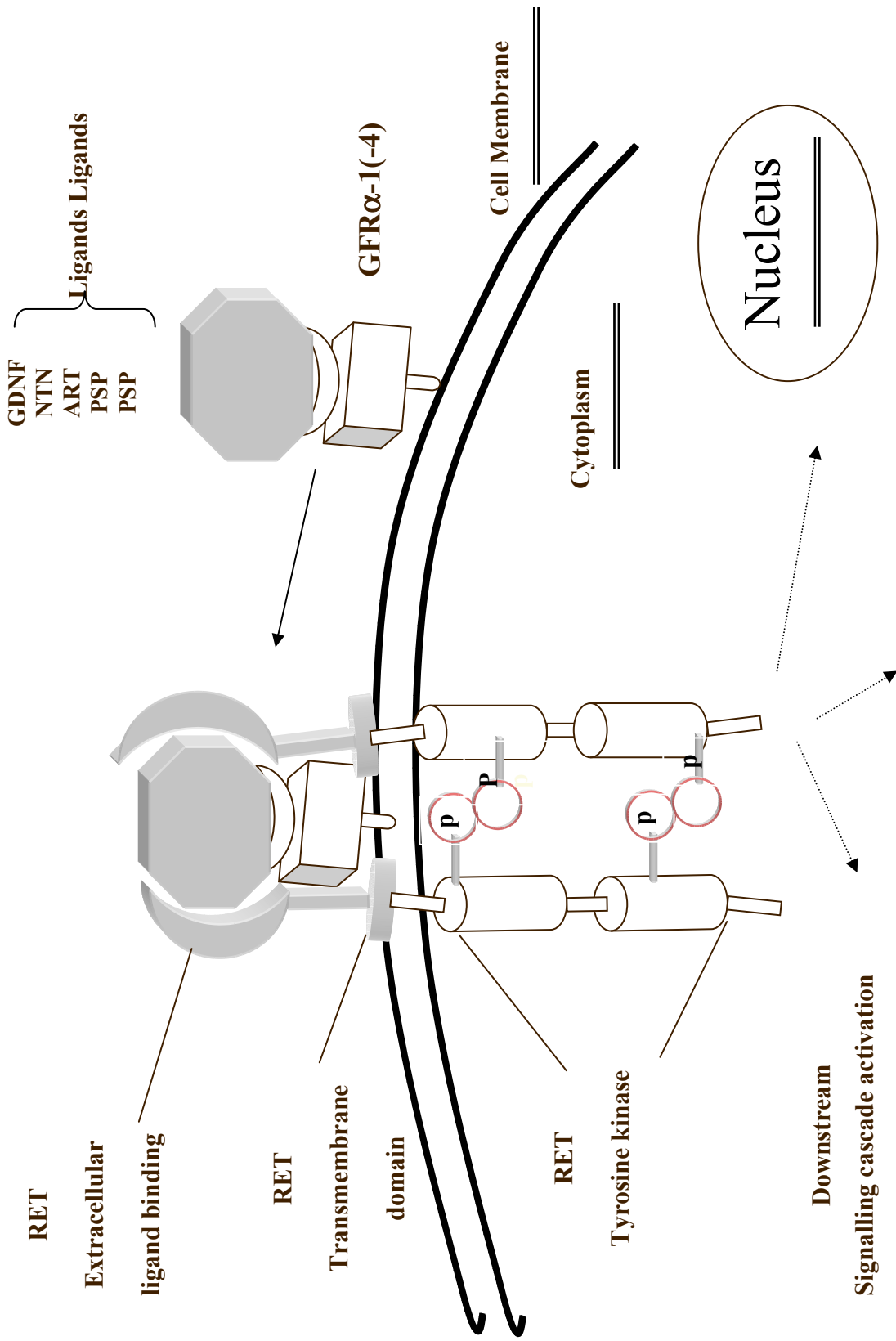
^c P > 0.9.

18.7. Summary

To understand the molecular genetics of human thyroid cancer, evidence-based medicine newly or only exists around Chernobyl. Therefore, it is the most important to establish and develop international collaborating projects to clarify not only the molecular mechanism but also the therapeutic strategies against human thyroid cancers, based on the understanding of its molecular genetics.

A straight line linking a specific class of carcinogenic factors, a specific type of molecular genetic alteration, and a specific group of cancers — the ultimate goal of molecular genetic epidemiology — can at least tentatively be drawn in the cohort of children exposed to the fallout of Chernobyl accident. Here, one of clear evidences of molecular genetics of human thyroid carcinogenesis is *ret/PTC* rearrangement, but still it is needed to be clarified that the direct cause-and-effect relationship of radiation-induced thyroid carcinogenesis. Careful and precise analysis of *ret/PTC* rearrangements [18.61] can simultaneously improve knowledge and clinical application of diagnosis and treatment for spontaneous thyroid cancer. Therefore, establishment of Chernobyl Thyroid Tumour Bank can promote the scientific cooperation to give us a clue of signature gene(s) and molecule(s) from the unique thyroid cancer tissues [18.62-18.63].

FIG. 18.1. Schematic representation of the RET gene product and its relationship from ligand binding to intracellular signal transduction. The RET receptor are glial cell-derived neurotrophic factor (GDNF), neurturin (NTN), neublastin/artemin (ART) and persephin (PSP), which are distant members of TGF β family [18.64]. They all activate a common signaling component, the RET tyrosine kinase receptor through the preferential binding to a co-receptor, which belongs to a novel class of glycoylphosphatidyl inositol membrane-linked proteins called GDNF family receptor α (GFR α). Four distinct GFR α have been described, GFR α 1 to 4, that respectively bind preferentially to GDNF, NTN, ART and PSP. The binding of ligand(s) to the RET receptor forms multimeric receptor complex that includes GDNF as one of the ligands, and its cell surface receptor; GFR α . The ligand binding to this receptor complex activates RET receptor tyrosine kinase, causing phosphorylation of specific substrates and stimulating the downstream signalling cascades, such as src, leading to cell proliferation.



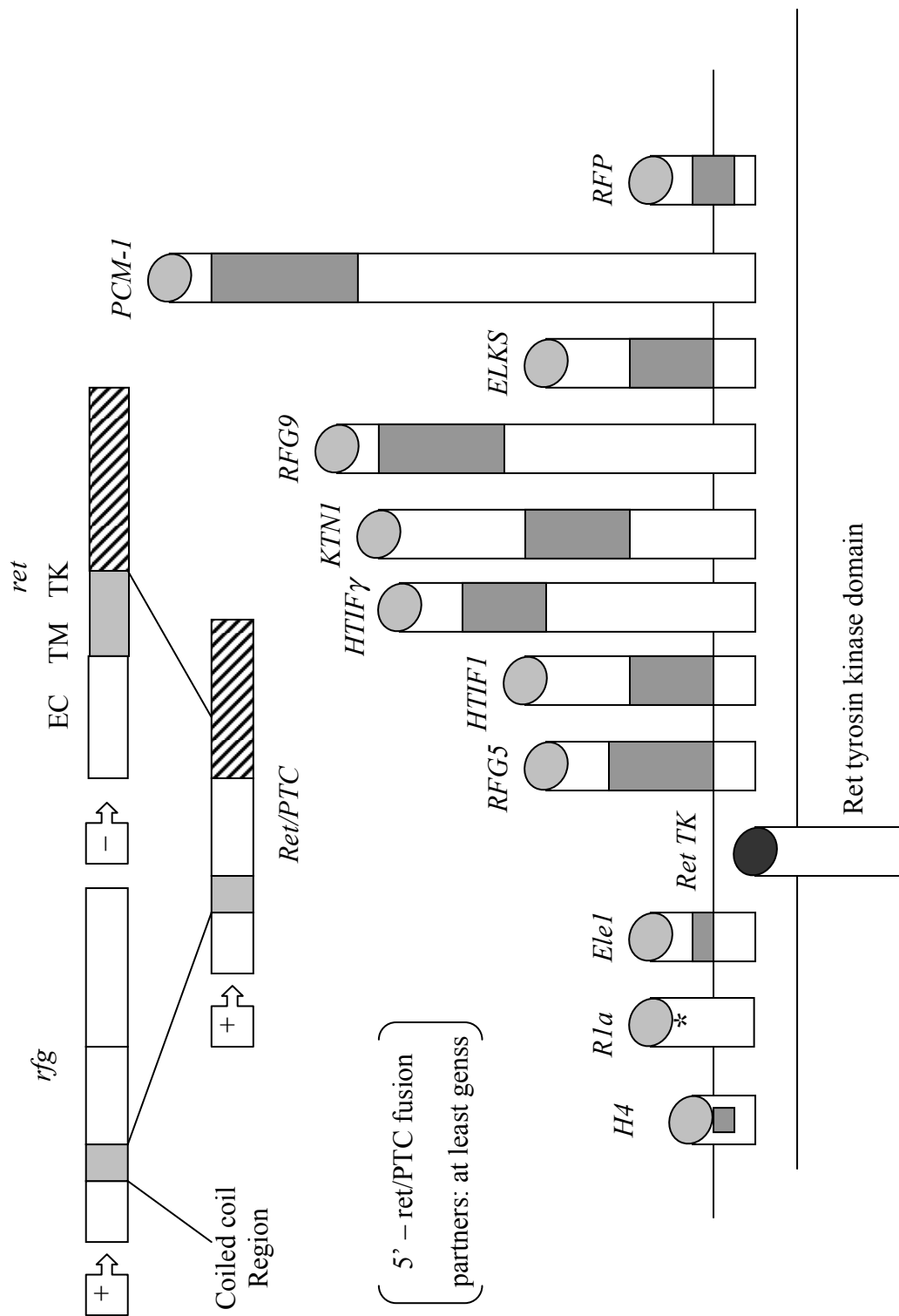
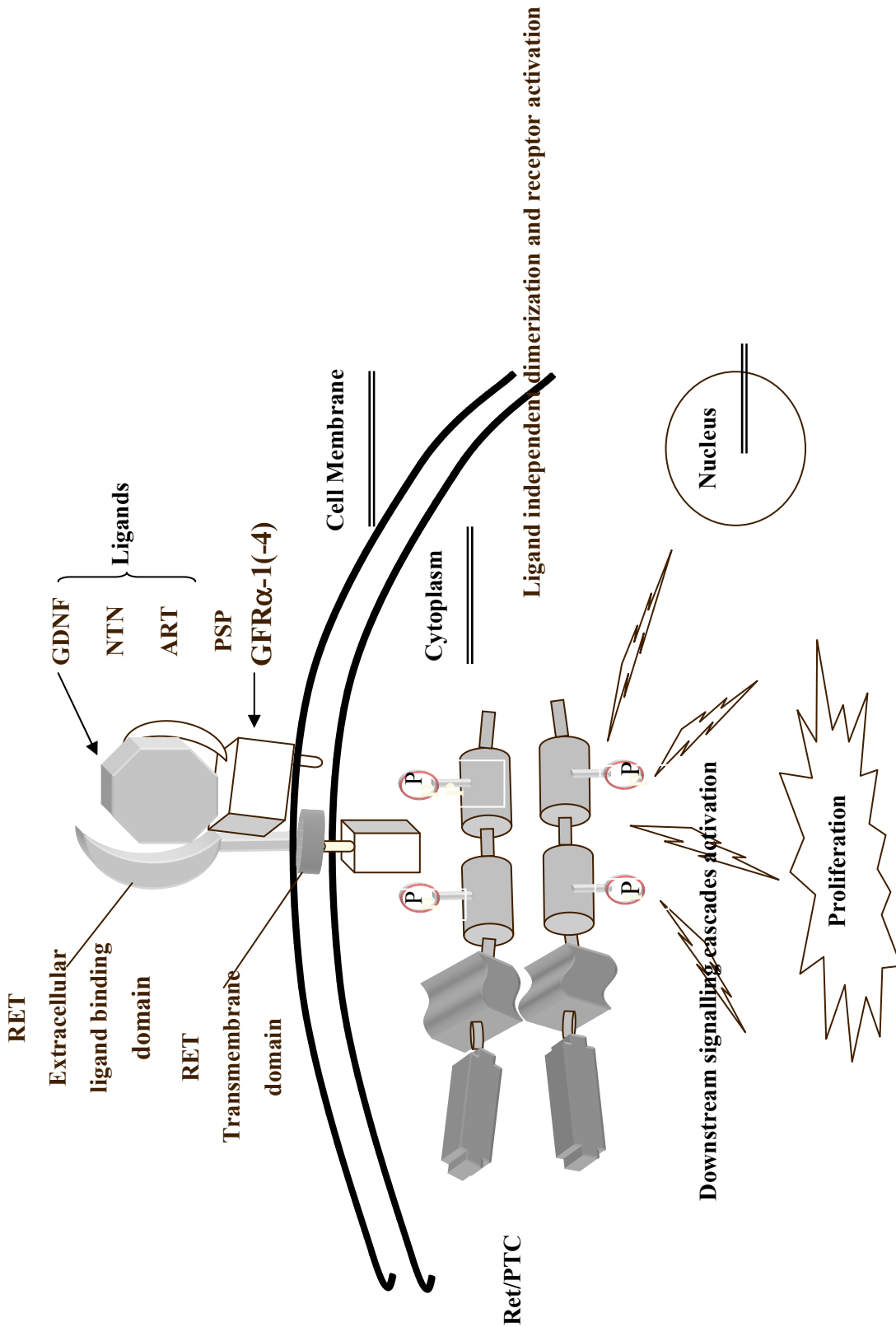


FIG. 18.2. The structural characteristics of *ret*/PTC rearrangements obtained from human papillary thyroid cancer tissues. These arrangements lead to the fusion of the Ret TK domain to 5'-terminal regions of heterologous genes, generating chimeric oncogenes referred to as *ret*/PTC. Eleven *ret* fusion partners are shown accounting for at least 16 different fusion proteins.

FIG. 18.3. Schematic representation of the *ret/PTC* fusion gene product and constitutive active signalling mechanism. Independent from extracellular signal regulation, the recombinant gene product *ret/PTC* exerts its function via intracellular dimerization through coiled-coil domains and stimulates intrinsic kinase activity. Abnormal cell proliferation and/or cell transformation are caused by ligand-independent receptor dimerization and constitutive activation of downstream signalling cascades.



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19. EMERGING STRATEGIES

19.1. Introduction

Despite important progress in the understanding of the molecular and cellular basis of thyroid tumourigenesis, documented by the publication of thousands of articles in the scientific literature, substantial improvements in the diagnosis and management of thyroid cancer are limited. In the last 30 years the most relevant achievement in the field of differentiated (papillary and follicular) thyroid cancer (DTC) has been the discovery that serum thyroglobulin (Tg) measurement is a specific and sensitive tumour marker [19.1] for the post-surgical follow-up. Its introduction in the clinical practice has greatly facilitated the identification of patients free of disease and of those with persistent or recurrent disease, after total thyroidectomy and thyroid ablation. The impact of serum Tg measurement in the clinical practice has been so straightforward that, nowadays, it is considered by most authors the most reliable and informative test in the process of decision making. In a totally different area, medullary thyroid cancer (MTC), an important achievement has been the discovery in 1993 that germline point mutations of the RET proto-oncogene are causative event in the pathogenesis of the hereditary form of MTC, one of the manifestations included in the Multiple Endocrine Neoplasm type 2 syndrome. Genetic screening of RET mutation in the constitutional DNA has allowed the early identification of MEN 2 gene carriers, and prophylactic thyroidectomy may now avoid the development of MTC in these subjects [19.2].

Recently, a major advance in the management of differentiated thyroid cancer has been the development of recombinant human TSH as an alternative to thyroid hormone withdrawal for monitoring patients treated with total thyroidectomy and thyroid ablation. This section will review the impact of rhTSH in clinical practice, trying to envisage how this new compound will change current practice of following differentiated thyroid cancer. In addition several other potential developments currently under implementation in both the diagnosis and treatment of thyroid cancer are discussed. Furthermore it will consider some of the controversies.

Controversial issues

- Primary diagnosis:
 - US vs $^{99m}\text{TcO}_4$ scan
 - Thyroid functions tests
- Extent of surgery
 - Lobectomy vs total thyroidectomy
 - Completion total thyroidectomy vs RAI ablation
- Risk stratification
 - Value of radio-iodine in ablation for remnants
 - Value of radio-iodine for small lesions
- High dose vs low dose
 - How high is high? How low is low?
- Pre-therapy or pre-ablation diagnostic scan
 - To do or not to do?
 - Stunning
- Combined use of radioiodine and radiotherapy
 - Tg-positive & iodine-negative cases
- Unifying protocols for post surgical follow-up
 - Dose limits for persisting disease

	Role of Lithium, Retinoic acid
	Gene manipulation of NIS
	Cost-benefit issues of post-therapy imaging modalities
	Role of rhTSH
Others	

19.2. Use of rhTSH in the diagnostic evaluation of differentiated thyroid cancer

Most neoplastic follicular cancer cells retain the ability to produce thyroglobulin and to take up iodine, upon stimulation by TSH. On this basis the traditional follow-up of differentiated thyroid cancer is based on the withdrawal of L-thyroxine, to induce a raise of serum TSH sufficient to induce the synthesis and secretion of serum Tg (as tumour marker) and to promote uptake of tracer doses of ^{131}I (as imaging procedure). Furthermore, when metastatic foci are localized, high doses of ^{131}I are administered with therapeutic intent. Unfortunately, withdrawal of L-T4 therapy is associated with a period of hypothyroidism sufficient to impair the quality of life in many patients [19.3].

The idea to use exogenous TSH stimulation, instead of endogenous stimulation, dates many years ahead, when injection of bovine TSH was used to stimulate thyroid cancer patients. The results were disappointing: the degree of stimulation was inadequate, side effects were frequent and, most of all, immunity against TSH did occur. After cloning of the human TSH gene [19.4], hyperexpression of its encoded protein has been induced in eucariotic cells by recombinant techniques, thus allowing the recovery of large amounts of highly purified recombinant human TSH (rhTSH, Thyrogen, Genzyme Therapeutics). As demonstrated by *in vitro* and *in vivo* studies, rhTSH overcomes the limitations of bovine TSH, since it is not immunogenic, it is deprived of relevant side effects and it is as effective as endogenous TSH stimulation in promoting both Tg stimulation and ^{131}I uptake [19.5, 19.6]. Based on the results of two extensive phase III clinical studies [19.7, 19.8], rhTSH has recently been approved for the diagnostic evaluation of patients with differentiated thyroid cancer. These studies have shown that rhTSH preparation for diagnostic ^{131}I whole body scan and Tg measurement is as effective as L-thyroxine withdrawal in detecting residual disease in virtually all patients.

Robbins, et al. [19.9] have confirmed these results in the clinical practice. They compared two groups of DTC patients undergoing follow-up for DTC after L-T4 withdrawal (161 patients) and after rhTSH (128 patients). The authors found that the results of diagnostic WBS and of stimulated serum Tg obtained with the two methodologies had the same positive and negative predictive value in the detection of residual disease. Based on these findings it is proposed that the follow-up of DTC patients may be based on periodical serum Tg measurement and ^{131}I uptake after stimulation with rhTSH, with the aim of selecting patients with persistent disease to be submitted to the more appropriate treatment. As after L-T4 withdrawal, patients with circulating anti-Tg antibodies may have falsely depressed serum Tg levels when stimulated with rhTSH. These patients may benefit only from the information derived from ^{131}I WBS after rhTSH and from the other common imaging techniques, including neck ultrasound.

There is much of agreement that serum Tg measurement is more sensitive than diagnostic WBS in detecting residual disease [19.10, 19.11]. Recently, the utility of routine use of diagnostic WBS in DTC patients treated with total thyroidectomy and post-surgical thyroid ablation, has been questioned. Two large retrospective series [19.12, 19.13] of patients undergoing routine diagnostic follow-up after L-T4 withdrawal, have shown that when serum

Tg is undetectable, the diagnostic WBS is always negative or may show marginal residual uptake in the thyroid bed, thus not adding any relevant information. After more than ten years of follow-up, the large majority of these patients were free of disease and local recurrence (metastatic lymph nodes) were detected, usually by neck ultrasound, in as little as 0.6% of the cases. Even when serum Tg is detectable, a significant proportion of patients (around 20%) may have false negative WBS. In most of these patients residual disease may be visualized in the post-therapy scan performed after the administration of high doses of ^{131}I (100-150 mCi) [19.10, 19.11, 19.14, 19.15]. On these basis, it is now possible to suggest the avoidance of the diagnostic WBS in patients with undetectable stimulated serum Tg levels (and negative anti-Tg antibodies), and to advocate ^{131}I treatment and post-therapy scan in those who have detectable basal or stimulated serum Tg levels.

The low clinical yield of diagnostic WBS compared to that of serum Tg measurement has been recently confirmed also when testing is performed after rhTSH stimulation. Pacini, et al. [19.16], in a prospective study in 72 patients with undetectable basal serum Tg concentration, found that the diagnostic WBS was not informative in the 41 patients with undetectable rhTSH-stimulated serum Tg and in 8 of the 31 patients who converted from undetectable to detectable after rhTSH. The conclusion of these authors was that in patients with undetectable basal levels of serum Tg, rhTSH-stimulated Tg measurement represents an informative test to distinguish disease-free patients (not requiring WBS) from diseased patients (requiring further diagnostic and/or therapeutic procedures).

Similar results have been reported by Mazzaferri and Kloss in 107 patients [19.17]. Also in this series the diagnostic yield of the WBS was very little compared to the information derived by the rhTSH-stimulated serum Tg measurement. Out of 107 patients who were clinically free of disease, 10% had persistent tumour that was only identified with an rhTSH-stimulated serum Tg level greater than 2 ng/ml. As reported in a recent Editorial by Wartofsky [19.18], altogether the available evidence is sufficient to propose a diagnostic follow-up of DTC patients based mainly on the use of rhTSH-stimulated serum Tg and post-therapy scan when ^{131}I treatment is indicated. Such an attitude will preserve the patients' quality of life by avoiding hypothyroidism and will save many unnecessary diagnostic WBS, reducing the need for imaging to the minority of patients with residual disease. Future studies directed to a more full definition of the use of rhTSH, particularly in the setting of ^{131}I therapy for thyroid ablation or metastatic disease, will further facilitate the diagnostic and therapeutic management of DTC patients.

19.3. Novel diagnostic and therapeutic strategies for poorly differentiated thyroid cancer

Normally, thyroid carcinoma is a disease with an excellent prognosis, but a significant proportion of patients (20-30%) display a poorly differentiated histotype in the primary tumour or dedifferentiate during the course of the disease and eventually develop into highly malignant phenotype up to anaplastic thyroid carcinoma. Due to the loss of thyroid-specific function, these tumours cannot be monitored with the usual diagnostic protocols and are insensitive to standard therapeutic procedures, such as ^{131}I therapy and thyroid hormone suppressive therapy. The prognosis of these patients is rather poor and, for its amelioration, new diagnostic and treatment options are urgently needed.

Traditionally, alternative imaging techniques may include CT scan and MRI of the chest and neck, bone scintigraphy, and other non specific isotopic scan (Thallium-201, technetium-99m, tetrofosmin). CT scan and MRI are the most used techniques to localize tumours in the neck,

mediastinum, chest and bones. Technetium-99m tetrofosmin [19.19] and technetium 99m Sestamibi [19.20] have been proposed as a useful method for the localization of metastatic Hürthle cell tumours. Unfortunately, none of these methods give the ideal sensitivity and specificity.

Positron emission tomography (PET) using fluorine-18 fluorodeoxyglucose (FDG) is a new imaging technique recently introduced in clinical practice, which seems to be promising [19.20-19.22]. The methodology is based on the enhanced glucose metabolism, observed as a non-specific feature of neoplastic cells, including poorly differentiated thyroid tumours. FDG uptake can be seen when the patient is on L-thyroxine therapy, although it was found to be higher when the patient is hypothyroid [19.23]. In a recent meta-analysis including data of a multicentric study in patients with Hürthle cell tumours, PET results were informative in detecting metastatic foci in almost all cases, with a sensitivity of 92%, a specificity of 80%, a positive predictive value of 92% and a negative predictive value of 80% [19.24]. The usefulness of FDG-PET has been investigated in well-differentiated thyroid cancer patients with negative ¹³¹I scan and elevated serum Tg levels. In two recent studies [19.25, 19.26], FDG-PET correctly detected metastatic disease in 94.6% of cases, influencing the therapeutic strategy in many cases. Altogether, these data indicate that FDG-PET is a promising imaging technique for the localization of residual or metastatic tumour in patients with poorly differentiated thyroid cancer and in well-differentiated thyroid cancer deprived of iodine uptake.

In the therapeutic setting, several research strategies are being implemented and some new therapeutic approaches are already entered into clinical trials. The most attractive models are aimed a) to re-induce a pattern of well differentiation in poorly differentiated or undifferentiated tumours, and b) to test the feasibility of gene therapy, following different strategies.

19.4. Redifferentiation therapy

Poorly differentiated tumours are characterized by the loss of expression of differentiation genes specific for the thyroid gland, such as the TSH receptor gene, the thyroglobulin gene or the NIS gene. The last is the gene responsible for the iodine uptake and its expression is frequently lower in thyroid cancer cells compared to normal follicular cells [19.27], and it is completely abolished in tumours no longer responsive to radioiodine therapy. The possibility to re-induce the expression of the NIS gene would render the tumours sensitive again to the effect of radioiodine. Retinoids are biologically active metabolites of vitamin A, with growth-inhibiting and differentiation-inducing properties. They have been used for treatment and chemoprevention of several human cancers (such as acute promyelocytic leukemia) and, recently, have been proposed as a potential agent of re-differentiation in thyroid cancer. In vitro, treatment of follicular thyroid carcinoma cell lines with retinoic acid (RA) exerted significant antiproliferative effect [19.28], elicited an increase of NIS mRNA expression and of iodine uptake [19.29, 19.30], and, by decreasing the extracellular matrix degradation, had beneficial effects on metastatic behaviour [19.31]. In vivo, 13-cis-retinoic acid (Roacutan) has been used in several limited series of poorly differentiated thyroid cancer with the aim to re-induce iodine uptake, at doses of 1.0-1.5 mg /kg body weight for 2-6 weeks. Re-induction of ¹³¹I uptake was observed in 5/12, 8/20 and 4/10 patients in three different series [19.32-19.34]. Altogether, the results of the in vitro and in vivo studies may be interpreted as evidence of redifferentiation, deserving more extensive clinical evaluation.

19.5. Gene therapy

The essential of gene therapy is the introduction of DNA into target cells. Although cancer is a multigenic disease, with more than one gene being dysfunctional, several oncogenes have been unequivocally associated with thyroid carcinoma, and may become the target for gene therapy. Several approaches have been specifically proposed in thyroid cancer [19.35].

19.5.1. Reintroduction of the p53 tumour suppressor gene

In tumours lacking a functional p53 gene (as it is the case of most undifferentiated thyroid carcinoma) may be one way to proceed. p53 is a tumour suppressor gene, normally devoted to arrest the cell cycle to allow repair of DNA damage or to induce apoptosis. When p53 is mutated, this mechanism is not working and cells with genomic alterations are free to survive and propagate. Reintroduction of p53 in thyroid carcinoma cell lines with p53 mutations converted the cells to a more differentiated phenotype. Expression of thyroid specific genes was stimulated, modulations by TSH was restored, tumourigenic potential was reduced and proliferation was inhibited [19.36-19.40]. So far, treatment of patients by this approach has been tested in a few patients with advanced lung carcinoma [19.41] but never in thyroid carcinoma.

19.5.2. Suicide gene therapy

With this approach, gene transfer is used to introduce into the tumour cells a vector coding for a 'sensitizing enzyme' that is able to activate a chemotherapeutic agent (pro-drug) only in the cells where the sensitizing enzyme is expressed. Several pro-drug/sensitizing enzyme systems have been tested for thyroid carcinoma in vitro [19.42].

19.5.3. Immunotherapy

Immune response against cancer antigens is somehow impaired in oncological patients due to a number of mechanisms. Using immunostimulatory agents enabling the host to enhance anti-cancer immunity is a promising strategy for cancer therapy. Experimental studies in vitro and in animal models by Zhang, et al. [19.43-19.45] have confirmed the feasibility of this approach in medullary thyroid carcinoma (MTC). They used a replication defective adenovirus to transduce MTC cell lines with the murine interleukin-2 (IL-2) gene under the control of the human cytomegalovirus promoter. After infection, murine (and human) MTC cell line secreted large amount of IL-2. When these cells were injected into syngeneic animals, IL-2 positive tumour cells showed a markedly reduced tumour growth. Furthermore, these authors were able to show that immunity against MTC cells was long-lasting and that the adenovirus vector used was safe on other organs.

Other potential approaches to gene therapy may be represented by genetic immunization (DNA vaccination) with tumour-specific genes (calcitonin, thyroglobulin in the case of thyroid tumours), antisense therapy (blocking the overexpression of c-myc, typical of several thyroid carcinomas) and reintroduction of the NIS gene in thyroid tumours lacking NIS gene expression.

In conclusion, although at the moment gene therapy is translated in little benefit for the patients, research in the area is rapidly progressing and the first results are encouraging to further pursue the goal of new therapeutic strategies.

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Annex I

MANAGEMENT ALGORITHMS

IAEA has conducted a number of Regional and National Training Courses/Workshops on thyroid diseases in various parts of the world. In November 2002, during the regional training workshop on Thyroid Cancer held in Philippines, it was decided to draw up an algorithm to guide the medical practitioners in the diagnostic steps and therapeutic manoeuvres to follow when dealing with a thyroid nodule (see Figs I-1, I-2 and I-3). This recommended algorithm is a compilation of the collective contribution of the participants based on their experiences and enriched by the amendments and suggestions of experts from various regions of the world together with numerous evidences cited by prominent authors.

The algorithm does not in any way claim extensiveness in the approach to a patient with thyroid nodule/s in the diagnostic work-up and treatment. The overriding consideration is that of making a simple, easy-to-follow protocol with minimum expense and utilizing what is usually available in most thyroid clinics in developing countries. The algorithm deals only with Solitary Thyroid Nodule (STN), the likely seedbed of most thyroid carcinomas, particularly the differentiated type. It tackles situations where the clinical history and physical examination suggest either high or low probability of malignancy in a given nodule. To be sure, there are exceptions to these categorizations and the physicians should exercise prudent clinical discernment and judgement.

Throughout this algorithm, diagnostic steps are depicted by diamonds while conclusions or action steps have been given in rectangles. Diagnostic test results or time elements are simply stated without corresponding symbols. Amounts of radioactivity are expressed in SI units followed by conventional units in parentheses. When not stated, medical follow-up and treatment are presumed with patients receiving levothyroxine (L-T4) which is taken uninterruptedly except when indicated prior to particular testing.

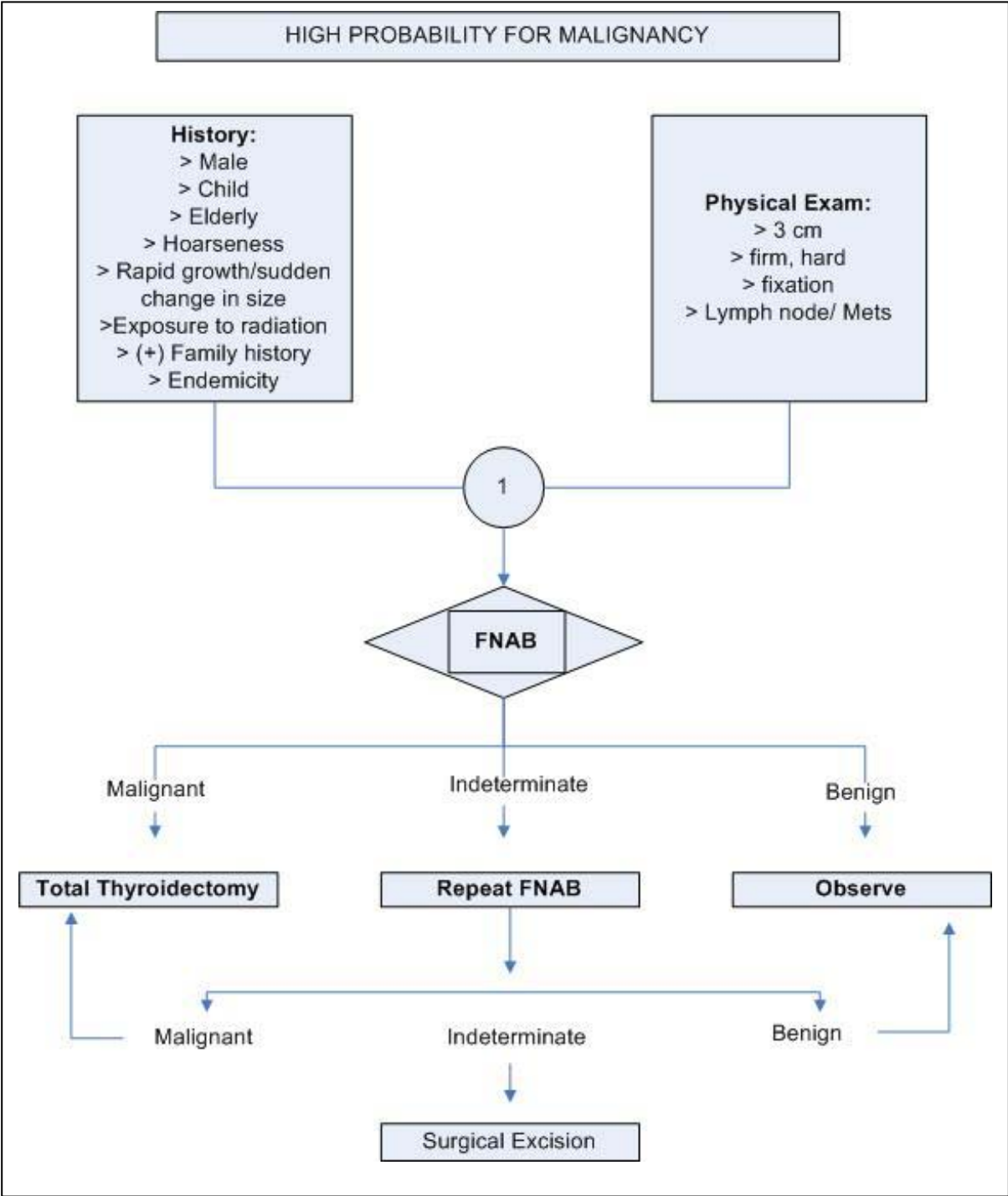


FIG. I-1. Solitary thyroid nodule — High probability for malignancy

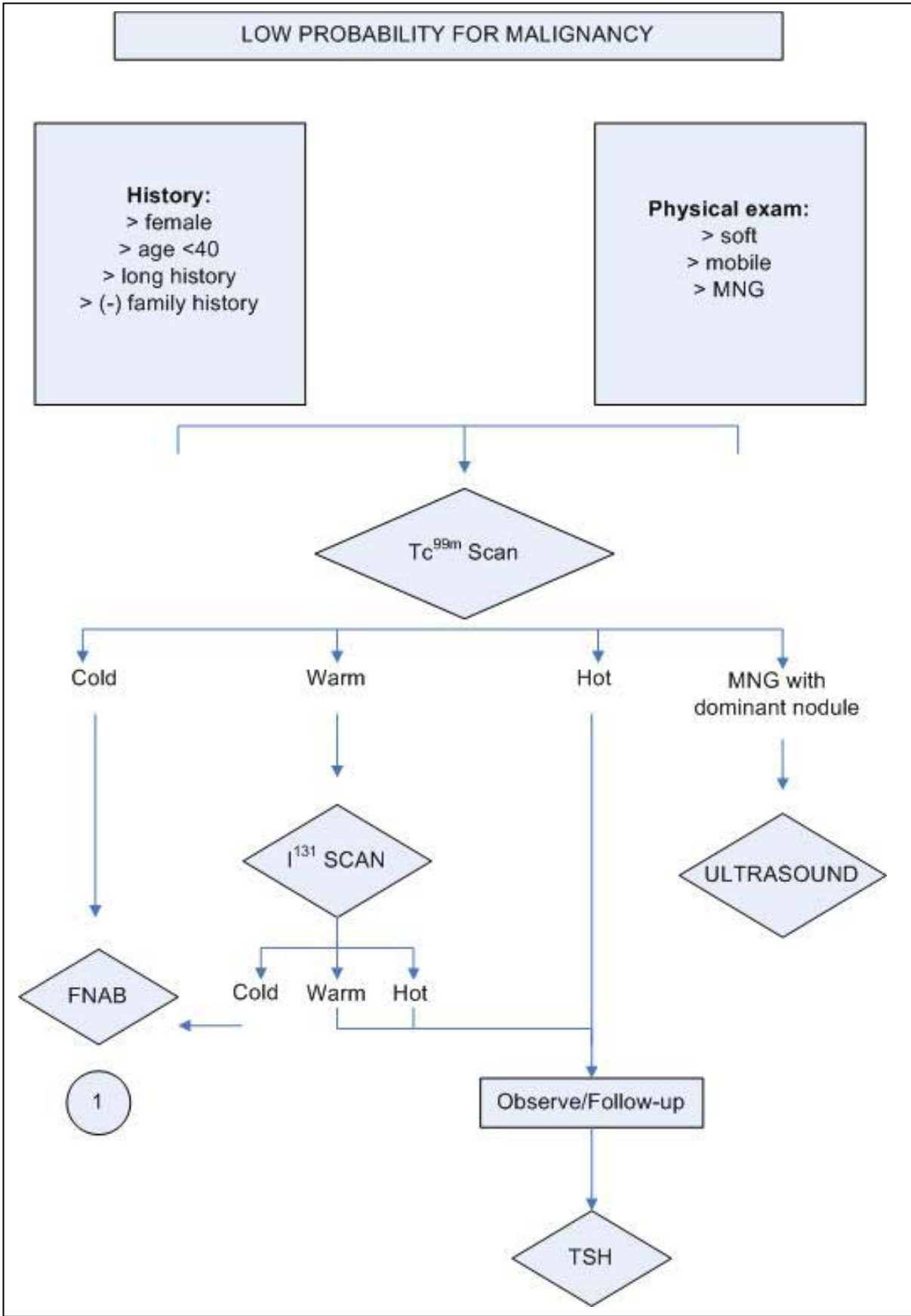


FIG. I-2. Solitary thyroid nodule — Low probability for malignancy

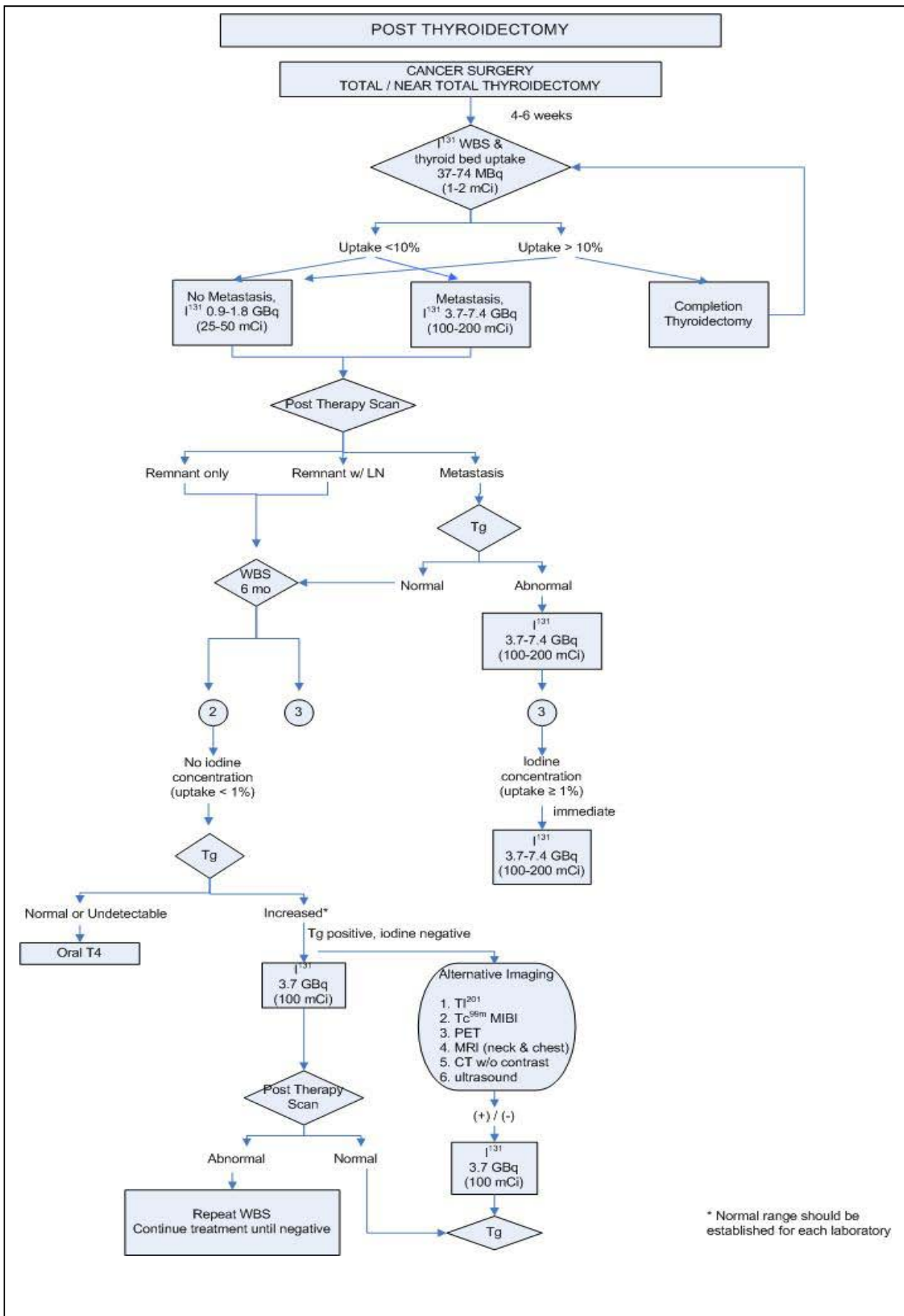


FIG. I-3. Post thyroidectomy

Annex II

SAMPLE PATIENT INFORMATION SHEET

¹³¹I THERAPY

WHAT'S IT ALL ABOUT?

WHAT IS A ¹³¹I THERAPY DOSE FOR?

! ¹³¹I therapy detects and treats any areas of residual thyroid tissue or tumour.

! The ¹³¹I causes very few side effects. You may experience some minor neck discomfort over the first few days. No other discomfort is likely, though you need to remain in an isolation room for an average of four days.

IS THERE ANY PREPARATION REQUIRED?

! For at least 1 month prior to ¹³¹I therapy you must not have had Iodine containing preparations (certain vitamin tablets, cough mixtures and kelp tablets) as well as X ray contrasts used for angiograms and CT scans.

! The isolation room is used to limit radiation exposure to other people. You will be instructed about certain simple precautions to undertake.

! Thyroid hormone medication will also need to be stopped for approximately 6 weeks before therapy. This will be arranged by your own doctor.

! The Hospital's Radiation Protection Officer will check your radioactivity level and will decide when you can be discharged home from hospital (usually three days after admission).

! In addition you require certain blood tests on the morning before ¹³¹I administration (to check whether any residual thyroid tissue is adequately stimulated, and a pregnancy test if you are a woman of childbearing age). These tests will be organized by your own doctors.

! Before you are discharged you will be brought to the Department of nuclear medicine where pictures of your body will be taken from various angles. Further delayed views may also be necessary.

! The ¹³¹I therapy dose is administered whilst you are in hospital. A hospital bed will be arranged for you.

! When you are discharged home you will be instructed as to certain simple precautions to take over at least the next 7 days. Any additional precautions will be discussed with you.

VERY IMPORTANT

IF YOU ARE OR COULD BE PREGNANT OR ARE BREAST FEEDING, PLEASE NOTIFY STAFF BEFORE PROCEEDING WITH THE THERAPY DOSE. YOU MUST ALSO NOT BECOME PREGNANT FOR AT LEAST 6 MONTHS AFTER THE ¹³¹I THERAPY DOSE.

1. Avoid close or prolonged contact with pregnant women or very small children. A good guide is to stay more than one arms length away from people.

2. Avoid unnecessary trips on public transport and attending public entertainment (you could be sitting next to someone pregnant).

3. Flush toilet twice after use. Wash hands copiously.

WHAT DOES A ^{131}I THERAPY DOSE INVOLVE?

! You will be admitted to a single room. A drug may be given to you prior to ^{131}I therapy to prevent potential nausea.

! A doctor and a technologist will come from the Department of nuclear medicine to administer the therapy dose. The doctor will check certain details (such as the date of surgery, and the result of any blood tests you may have had).

! You will then be asked to swallow a capsule containing the Iodine-131. This radioisotope is accumulated by areas of thyroid tissue and destroys these areas.

4. Do not attend work if this involves prolonged contact with people.

5. If convenient sleep in a single bed if partner is less than 50 years of age.

6. Wash hands carefully before preparing food. Do not share your utensils with other family members and avoid activities which may involve exchange of saliva (e.g. kissing).

7. If you are admitted to hospital within 4 weeks of the dose, please arrange for the nuclear medicine department to be notified.

Annex III

SAMPLE DOSE ADMINISTRATION RECORD

DEPARTMENTAL ¹³¹I ADMINISTRATION PROCEDURE

1. PATIENT ID

PATIENT WRIST BAND AND/OR NAME CHECKED

2. PREGNANCY

IF OF CHILD BEARING AGE RECORD SERUM BETA-HCG

RESULT DATE

3. MEDICATION

ANTI-NAUSEA PREMEDICATION GIVEN

THYROXINE WITHDRAWN FOR ADEQUATE TIME

PLEASE RECORD THE TSH RESULT

4. DOSE

CORRECT DOSE OF I¹³¹ IS AVAILABLE

5. INFORMATION

THE PATIENT HAS RECEIVED ADEQUATE INFORMATION AND UNDERSTANDS THAT IT IS IMPORTANT TO SWALLOW (NOT CHEW) THE ¹³¹I CAPSULE

6. OTHERS

THE NECK WOUND IS NOT DISCHARGING

THE PATIENT DOES NOT SUFFER FROM INCONTINENCE

THERE IS NO DIFFICULTY SWALLOWING TABLETS OR VOMITING

I,.....

of.....

request ¹³¹I therapy to be given to (patient's name).

My condition and the need for ¹³¹I therapy have been explained to me by my doctors.

I understand that rarely complications occur and I accept the possible risks associated with the proposed ¹³¹I therapy. The reported side effects such as salivary gland and neck discomfort, nausea, changes in taste, bone marrow depression, risk of salivary gland tumours and possible risk of leukaemia have been discussed with me.

I have had the opportunity to ask questions about the ¹³¹I therapy and side effects and I am satisfied with the information I have received.

FOR FEMALES only.

I understand that it is important not to be pregnant or breast feeding at the time of ¹³¹I therapy or within 6 months afterwards..... (initials).

.....

Signature of patient/guardian/relative

(Delete as appropriate)

.....

Signature of witness

.....

Full name of witness

.....

Date

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