Annex IX of Technical Volume 4
INTRODUCTION TO RADIATION EFFECTS ON THE THYROID

IX–1. BACKGROUND

The thyroid is an endocrine gland situated in the neck that produces hormones that circulate in the blood and have effects on various tissues in the body. The principal effect of thyroid hormones is to regulate the body's metabolism. The thyroid is composed of two epithelial cells types, the follicular cells and the C cells. The C cells are responsible for the secretion of calcitonin and are involved in the regulation of bone metabolism. Structurally, the gland is composed of spherical follicles, which comprise a single layer of follicular cells, and a lumen filled with colloid. The colloid contains a large molecular weight protein, called thyroglobulin, within which the iodine containing thyroid hormones tri-iodothyronine (T3) and thyroxine (T4) are stored until they are released into the circulation. The C cells are found in the centre of the thyroid gland and sit behind the follicular cells lining the lumen of the follicle. The thyroid follicular cells are responsible for secretion of both thyroglobulin and T3 and T4.

The stable (non-radioactive) form of iodine (^{127}I) is present at low levels in the natural environment and is ingested in food and passes into the bloodstream. In order to ensure that there is always a sufficient amount of iodine for thyroid hormone production, the thyroid exploits a mechanism that both concentrates iodine from the circulation, and binds it within the follicular lumen. There is a natural transport of iodine in and out of the gland. According to the biokinetic model used by the International Commission on Radiological Protection (ICRP) [IX–1], about 30% of the iodine in blood is transferred to the thyroid, while the rest is excreted in urine. The iodine is retained in the thyroid of adolescents and adults with a biological half-life (the time taken for half of the atoms of iodine entering the follicular cell to pass back out as organic iodine) of 60–80 days. For children, the available human data show that iodine is retained in the thyroid with shorter retention times. There are certain conditions that may increase (iodine deficiency, hyperthyroidism) or decrease (iodine excess, hypothyroidism) the uptake of iodine by thyroid.

The follicular cells could give rise to two distinct morphological types of differentiated thyroid cancer (DTC) — papillary and follicular cancer. The two morphological types show differences in both molecular biology and clinical characteristics. Patients with DTC usually present with a palpable lump in the neck, swollen lymph nodes in the neck, or difficulty swallowing. The most common form (about 80%) of thyroid cancer is papillary thyroid cancer (PTC).

The usual treatment of DTC is by surgery to remove the thyroid gland or part of it. This is often followed by administration of high doses of ^{131}I to destroy the remaining thyroid cells. The ^{131}I therapy relies on the thyroid follicular cells functional ability to take up and bind iodine thus providing a mechanism for highly specific targeted clinical treatment. Thyroid surgery is not without its risks, which can include damage to the laryngeal nerve, affecting speech, or accidental removal of the parathyroid glands resulting in complications in calcium metabolism. Removal of the whole gland mandates administration of oral thyroid hormone replacement, the level of which requires monitoring throughout the rest of the patient's life.

With timely diagnosis and appropriate therapy (surgery with or without ^{131}I treatment) PTC has excellent prognosis with a mean 20 year survival rate of about 95% [IX–2, IX–3]. The survival rate of PTC depends on age and is particularly high for young onset PTC. A recent review of clinical outcomes in paediatric papillary carcinomas related to the Chernobyl accident suggests that the 30 year survival is 99%, despite the fact that around 30–50% of these patients may suffer a recurrence, 80% of these being in the thyroid bed or associated cervical lymph nodes [IX–4]. Even non-total thyroidectomy or lobectomy without ^{131}I treatment shows excellent prognosis (more than 95% survival) if the preoperative conditions of patients are adequately evaluated [IX–5, IX–6].

There remains some controversy about treatment strategy for PTC under 10 mm diameter, often referred to as microcarcinoma [IX–7 to IX–10]. Several observational studies have shown that only a small proportion of these tumors progress (evidenced by an increase in size, or the appearance of nodal metastases) over an average of 75 months, but progression is more common in younger patients (age under 40 at diagnosis) than older ones (age over 60 at diagnosis) (8.9% versus 1.6%) [IX–11]. In addition, high prevalence of thyroid microcarcinoma incidentally found at autopsy provides evidence that many of them may never become clinically relevant [IX–8]. For example, in Japan the reported prevalence of thyroid microcarcinoma at autopsy range between 10.5% [IX–12] and 19.7% [IX–13]. Thus, the risks from surgical treatment for any individual with microcarcinoma must be balanced with the risks of progression of disease.

Figures on the incidence of thyroid cancer are derived from data collected by population or hospital based cancer registries concerning patients who have been operated upon for the disease. The majority of these patients will have presented with some form of symptom prior to operation. The background risk of thyroid cancer in females is on average three times higher than in males and sharply increases with age, although the shape of this increase is gender specific. The incidence of thyroid cancer in those under 15 years of age at diagnosis is very low, varying between 0.5 and 1.5 per 1 000 000 per year worldwide [IX–14]. In Japan, the incidence rate of thyroid cancer in females rises sharply between 15 and 45 years of age, largely levels off between 45 and 75 years at around 15–20 cases per 100 000 per year and declines thereafter (Fig. IX–1). In males, there is a steady rise in incidence with age of 10-12 cases per 100 000 per year until about 75 years. The mortality rate for DTC is very low in children and young adults, but starts to increase steadily from 50 years of age in both females and males [IX–15]. The sex–age patterns of thyroid cancer incidence and mortality in other countries are generally similar to those in Japan. In addition, similar sex–age patterns are observed for non-malignant thyroid diseases that are far more common than thyroid cancer.
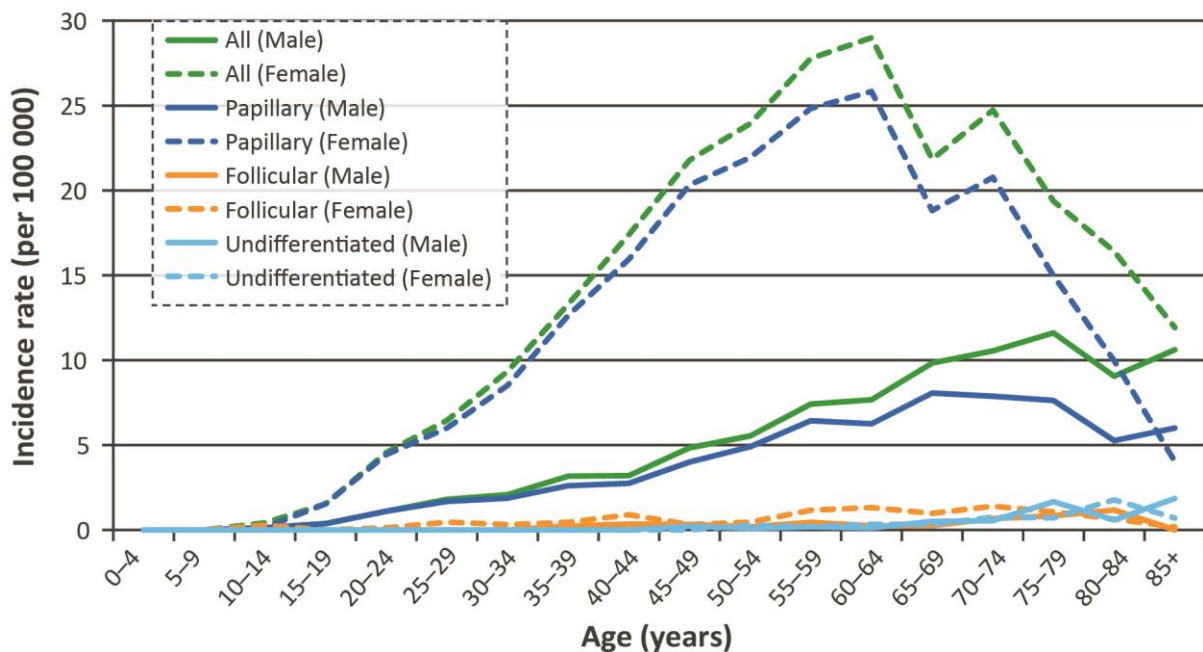

FIG. IX–1. Rate of incidence of age specific thyroid cancer (Japan). (Source: Miyagi, Yamagata, Fukui and Nagasaki Cancer Registries ICD10 Code: C73) [IX–16].

Thyroid cancer incidence in adults has been increasing steadily worldwide over the last 30 years. As this increase is primarily driven by PTC (the most common histological type associated with slow growth rate) and small size tumours, there is a view that improved determination through the greater

use of ultrasound equipment might have contributed to this trend [IX–8, IX–17 to IX–21]. Indeed, based on autopsy studies of thyroid microcarcinoma [IX–12, IX–13], one can expect an increase in thyroid cancer rates in an asymptomatic population undergoing thyroid screening with a sensitive instrument. It should be noted, however, that the resulting increase in incidence may not necessarily translate to decreased mortality [IX–17, IX–20, IX–21]. There is a considerable interest in trying to quantify the effect of screening on thyroid cancer rates in a given population. While it is widely appreciated that the magnitude of this effect will depend on characteristics of the screening instrument, it is often overlooked that it also depends on the characteristics of the population itself. For example, screening of two populations with the same instrument may result in different screening effects if a ratio of clinically apparent to pre-clinical cancers in these populations is different. The typical effect of screening is increased rates of early stage cancers due to the advance in the time of diagnosis. It is important to be aware of these issues when considering the results of the Thyroid Ultrasound Examination (TUE) carried out as part of the Fukushima Health Management Survey (see Section 4.4.5.4).

IX–2. EFFECTS OF RADIATION ON THYROID CANCER INCIDENCE AND COMPARISONS WITH THE CHERNOBYL ACCIDENT

In the event of an accident at a nuclear power plant, should there be a loss of containment, a number of different radionuclides might be released into the environment. Volatile radioisotopes of iodine and caesium, once dispersed in the air, can be inhaled or deposited on the ground. External exposure to radiation can occur from radioisotopes that remain outside the body. In addition, radioactive isotopes settled on food crops or on pastures on which farm animals feed may enter the human food chain (unless preventive measures are taken) and expose body organs and tissues internally. If ingested, radioisotopes of iodine would concentrate in the thyroid, whereas radioisotopes of caesium would distribute homogeneously throughout the body including the thyroid gland. Assessment of the doses to infants from radioiodine from the Fukushima Daiichi accident suggests that the contribution from isotopes other than ^{131}I is small (see Section 4.2.2). Following a review of external radiation studies, the remainder of this section is focused on the effects of ^{131}I on the thyroid. The long biological half-life of iodine in the thyroid (60–80 days) relative to the physical half-life of ^{131}I (8.1 days), suggests that an ingestion of ^{131}I with incorporation in the thyroid will deliver almost all of its radiation dose to the follicular cells of the thyroid gland, with very little ^{131}I re-entering into the circulation.

The thyroid glands of children are among the most radiosensitive of organs. There are abundant epidemiological data on the risk of thyroid cancer following exposure to radiation in childhood. Data for external exposure come from studies of atomic bomb survivors and medical exposures. For internal exposure from ^{131}I there is much information from studies that followed the Chernobyl nuclear power plant accident.

A 1995 pooled analysis of individuals exposed to atomic bomb radiation or medical radiation under 15 years of age remains one of the most informative studies in the field [IX–22]. In that study, the overall excess relative risk (ERR) of thyroid cancer was 7.7 per Gy (95% CI: 2.1-28.7) and linearity best described the dose response down to 100 mGy. If one study with very high risk was excluded or exposure status was adjusted for that study, the ERR per Gy was reduced to 3.8 (95% CI: 1.4–10.7). The ERR per Gy significantly varied by age at exposure even within this limited age range, with children exposed under one year of age having ERR per Gy five times higher than children exposed at 10–14 years. In a recent study of thyroid cancer incidence among atomic bomb survivors during 1958 and 2005, thyroid cancer cases (excluding those with microcarcinoma <10 mm in diameter) were analysed [IX–23]. Using a linear dose–response model, the ERR at 1 Gy of radiation exposure was estimated as 1.28 (95% CI: 0.59–2.70) at age 60 after acute exposure at age 10. The risk decreased sharply with increasing age at exposure and attained age. There was little evidence of increased thyroid cancer rates for those exposed after age 20. The BEIR VII model for risk of radiation induced thyroid cancer is based on the 1995 pooled analysis [IX–24]. This model predicts a lifetime sex-

averaged excess of about 250 thyroid cancer cases per 100 000 individuals[1] exposed to 100 mGy at age 5 relative to 67 cases per 100 000 individuals exposed at age 20.

Following the Chernobyl accident in 1986, large populations in Ukraine, Belarus and the Russian Federation were exposed to ^{131}I due to consumption of food containing ^{131}I [IX–25]. The subsequent dramatic increase in incidence of thyroid cancer, observed as early as 1991, was largely attributed to ^{131}I exposure [IX–26]. Descriptive studies evaluating rates of paediatric thyroid cancer in children exposed to fallout from the Chernobyl accident and those born nine months after the accident (and thus not exposed to radioiodines) found that after adjustment for sex and age cancer rates in exposed children were at least ten times higher. In addition, the rates of paediatric thyroid cancer in children born nine months after the accident and residing in the areas contaminated by caesium were comparable with the respective pre-accident rates. Together, these findings suggested that radioiodines rather than long-lived isotopes of caesium were responsible for the post-Chernobyl increase in thyroid cancer incidence [IX–27 to IX–29]. Later analytic studies with individual thyroid dose estimates established that increase in incidence of thyroid cancer depended on ^{131}I dose. In a prospective cohort of about 12 000 individuals exposed to ^{131}I <18 years of age in Ukraine, there were 65 thyroid cancers diagnosed up until the end of 2008 [IX–30]. The noteworthy features of this study include availability of individual radioactivity measurements taken soon after the accident and standardized thyroid screening irrespective of dose. It was found that the increase in ^{131}I-related thyroid cancer risk persists for two decades after exposure (ERR per Gy = 1.9; 95% CI: 0.4-6.3), with no evidence of decrease during the observation period. Similar findings were reported for prevalent thyroid cancer in a parallel cohort study in Belarus [IX–31]. The estimates of ERR per Gy reported by major post-Chernobyl studies of those exposed to ^{131}I in childhood range from 2 to 9 and are largely comparable to risk estimates from external radiation [IX–25]. However, many of these studies did not measure thyroid dose directly.

In contrast to childhood irradiation, the informative data concerning thyroid cancer risk following adult exposure are limited. In atomic bomb survivors, there was no significant increase in thyroid cancer risk in those exposed over the age of 20 [IX–23]. Several studies of populations exposed to high doses of radiation for therapeutic or diagnostic purposes also found no increase in thyroid cancer risk. A study of patients treated with external radiation for Hodgkin's lymphoma reported that patients irradiated at more than 20 years of age showed a significantly lower risk than those irradiated at younger ages. No increased risk for thyroid cancer was reported for those irradiated over the age of 35 [IX–32]. Furthermore, a significant increase in thyroid cancer was not observed in several hundred thousand patients with Graves' disease treated with about 5 mCi[2] (2×10^8 Bq) of ^{131}I. In this study, the reported relative risk (RR) was elevated, although not significantly so (RR = 1.58; 95% CI: 0.91–2.75) [IX–33]. Similarly, no increased risk of thyroid cancer was found in 24 010 adult patients without history of radiation therapy to the neck who received ^{131}I (mean = 0.94 Gy) for diagnostic purposes other than suspicion of a thyroid tumour [IX–34]. There have been few studies of thyroid cancer following low dose radiation exposure in adulthood. Study of cancer incidence in the National Registry for Radiation Workers in the United Kingdom, found a non-significantly elevated ERR per Sv for thyroid cancer of 3.24 (95% CI: –0.48–17.51) [IX–35]. A case control study of thyroid cancer in Chernobyl liquidators from the Baltic States, Belarus and the Russian Federation [IX–36] estimated an ERR of 0.38 per 100 mGy (95% CI: 0.10-1.09). As the recall bias and uncertainties in thyroid doses could have affected the magnitude of radiation risk in liquidators, further studies with more accurate dosimetry would be needed to validate these results. In general, available studies suggest that radiation risk of thyroid cancer following adult exposure might be substantially lower than following childhood exposure, although its magnitude remains uncertain.

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[1] These data relate to the population of the United States of America.

[2] mCi = millicurie.

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Hypothyroidism, a condition in which the thyroid gland does not make enough thyroid hormones, can develop from large thyroid doses of radiation due to destruction of a substantial proportion of the follicular thyroid cells. A small number of cases of clinical hypothyroidism were noted in Chernobyl cleanup workers who received large thyroid doses. However, the majority of these cases returned to euthyroid state over a period of five years [IX–25]. There are reports that clinical or subclinical hypothyroidism in non-exposed individuals can increase the likelihood of thyroid cancer in both children [IX–37] and those aged over 45 [IX–38] with pre-existing nodular disease. Whether the history of hypothyroidism is associated with increased risk of thyroid cancer in individuals without thyroid nodules remains debatable. The thyroid doses that could give rise to hypothyroidism are much higher than those received by the population of Fukushima Prefecture and the vast majority of the emergency workers at the Fukushima Daiichi power plant itself.

The effects of iodine insufficiency from living in an area where the levels of stable iodine (^{127}I) are low in the environment may increase the uptake of radioisotopes of iodine released from a nuclear accident, thus increasing thyroid doses [IX–1]. In addition, several post-Chernobyl studies found that, for the same absorbed dose of ^{131}I, the risk of thyroid cancer in iodine deficient areas is two to three times higher than in areas with adequate iodine intake [IX–39, IX–40]. In contrast to the populations of Belarus, Ukraine and the Russian Federation affected by the Chernobyl accident, the Japanese population resident in the areas around the Fukushima Prefecture is considered to be iodine replete.

Overall, it is to be expected that the incidence of radiation induced thyroid cancer following the Fukushima Daiichi accident will be less than was the case for the Chernobyl accident. The amounts of ^{131}I and ^{137}Cs released from the Fukushima Daiichi accident were considerably less than those released from Chernobyl [IX–41].

Moreover, the prompt action by the Japanese authorities to reduce exposure to radioiodine by evacuation, sheltering and severing the food-chain to prevent consumption of contaminated food reduced still further the exposure of the population of the affected area to both ^{131}I and ^{137}Cs [IX–42 to IX–44]. Additional reduction of dose to the thyroid was achieved by the administration of stable iodine but, as discussed in Technical Volume 3, it appears that this was carried out only in some areas and not in others so that the benefit of the stable iodine programme was not optimal.

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