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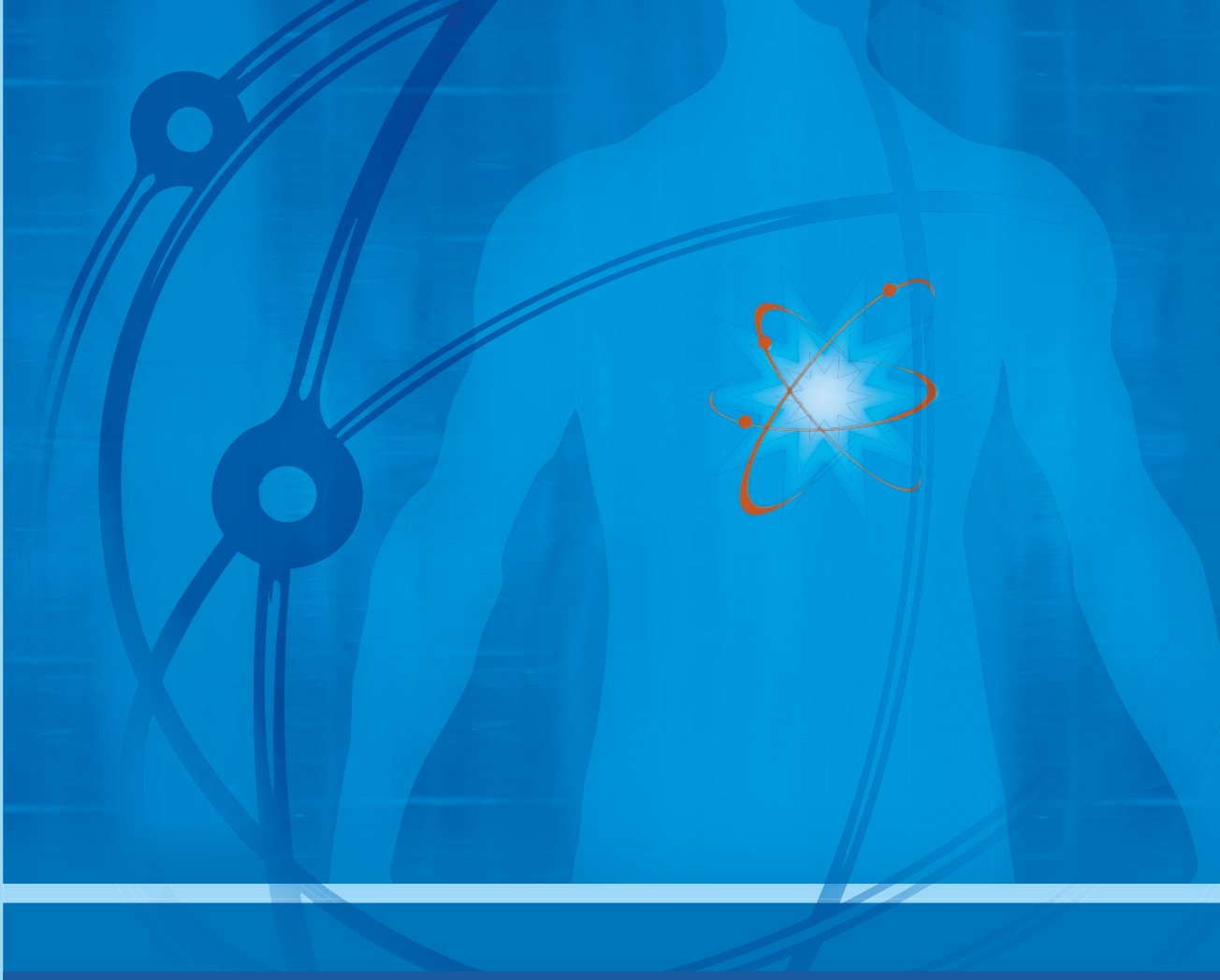

Strategies for the Management of Localized Prostate Cancer: A Guide for Radiation Oncologists

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STRATEGIES FOR THE MANAGEMENT OF LOCALIZED PROSTATE CANCER: A GUIDE FOR RADIATION ONCOLOGISTS

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FOREWORD

Prostate cancer is a serious health issue, especially considering the recent epidemiological trend and its corresponding socioeconomic impact. Challenges encountered by treating physicians include the long natural history of the disease, the fact that it is more prevalent in the elderly and the difficulty in performing a complete critical review of medical evidence due to the plethora of available information. In addition, the difficulty in deciding if and when therapeutic intervention should be initiated is an important issue pertaining to this type of malignancy. However, there is one area where there is a uniform consensus: the applicability of the multidisciplinary approach in the management of prostate cancer.

Clinical guidelines are systematically developed statements designed to help practitioners, managers and patients make decisions about appropriate health care for specific circumstances. Clinicians need simple, patient specific, user friendly guidelines. The main purposes of clinical guidelines are to: (a) provide recommendations for the treatment of individual patients by practitioners; (b) help develop standards to assess the individual practice of health professionals; (c) be used in the education and training of health professionals; (d) assist patients in making informed decisions; and (e) improve communication between patients and health professionals.

Clinical guidelines for the management of prostate cancer exist in the published literature. However, these guidelines have usually been developed in and for affluent health care environments where all modern diagnostic and treatment modalities are available. In limited resource environments, the radiation oncologist is faced with the question of what the minimum acceptable (evidence based) line of action would be, considering the limited resources available. Clinical guidelines focusing on low to middle income countries aim to provide these practitioners with a practical tool. This publication is aimed at radiation oncologists working in centres with limited resources who are treating a large number of patients with prostate cancer on a daily basis. The approach and techniques recommended are intended to be simple, feasible and resource sparing to the extent possible when dealing with a complex treatment modality. They take into consideration the cost–benefit ratio of the intervention to avoid the unnecessary overtreatment of indolent tumours.

The IAEA officer responsible for this publication was E. Zubizarreta of the Division of Human Health.

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1. INTRODUCTION

This publication is not designed to be a comprehensive work on prostate cancer oncology. It has been conceived as a practical manual for radiation oncologists treating large numbers of prostate cancer patients in a limited resource setting.

A number of guideline documents are available in the published literature for the management of common cancers. Large academic institutions typically produce their own local guidelines and use them regularly. In this telecommunication era, a wealth of information is readily available to those who have access to a computer and internet connectivity. Nevertheless, the Division of Human Health of the IAEA perceives a need for guidelines addressed to Member States with limited resources.

The IAEA has a unique mandate in the application of nuclear techniques in human health including radiotherapy. A long tradition of support to radiotherapy centres worldwide derives from Article II of the IAEA Statute: "The Agency shall seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world."

As opposed to large academic institutions or private centres in affluent health care environments, the radiation oncologist practising in a resource limited setting is faced with a different reality. The paucity of resources is reflected in the limited availability of treatment equipment and quality assurance equipment. Shortage of trained staff in sufficient numbers is a chronic problem in the developing world. There is limited, if any, access to published literature, and in many regions the language barrier is an additional problem.

Professionals with Internet access are faced with an enormous amount of information from which it is difficult to prioritize as to what is the acceptable care and what is feasible with the resources available. In addition, the transition from conventional 2-D treatment planning to 3-D conformal radiotherapy is creating the need for technical guidance to professionals working in smaller resource limited centres.

Therefore, in our work with low to middle income countries, we are regularly faced with the need for concise, clear and evidence based guidelines on radiotherapy treatment. Ideally, for common cancers, these guidelines should be available in the local languages.

Many IAEA guidelines on the treatment of cancers and commonly encountered clinical situations (e.g. painful bone metastasis, radiotherapy for palliation) are directed to the radiation oncologist practising in an environment with relatively limited resources. Such radiation oncologists are usually confronted with a large number of patients who require, and deserve, adequate radiotherapy. For this target audience, IAEA guidelines provide:

— Simple and concise sets of recommendations;
— Recommendations which are evidence based;
— Practical advice on how to perform procedures;
— Recommendations initially produced in English, which will be translated into other United Nations official languages for use in non-English-speaking Member States.

The methodology followed when producing these guidelines consisted of defining the objectives and scope, preparing a work plan, forming and conducting an expert consultant group, selecting the clinical questions, identifying the published evidence, reviewing and grading the evidence, making group decisions and reaching consensus, linking the guidelines to other guidelines on the subject, creating guideline recommendations, writing the draft guidelines, consulting within and outside of the expert group, editing and final checking before publication.

Users are encouraged to adapt the guidelines to the realities of their own region and/or culture. As they recognize that the accumulation of evidence is a dynamic process and that concepts and procedures in radiation oncology often change with time, the contributors to this publication feel that these guidelines will need to be updated in the future.

2. EPIDEMIOLOGY

According to the World Cancer Report 2008, prostate cancer is the most common cancer diagnosed in males in developed regions (643 000 cases, i.e. 20.2% of total new cancer diagnoses) but only the sixth most common cancer diagnosed in less developed countries (197 000 cases, i.e. 5.6% of total new cancer diagnoses) [1, 2]. Table 1 presents data on the incidence of prostate cancer around the world collected by the regional offices of the World Health Organization (WHO), as reported in GLOBOCAN 2008 [2].

TABLE 1. INCIDENCE RATES OF PROSTATE CANCER REPORTED BY WHO REGIONAL OFFICES

WHO Regional Office for:	Crude incidence rate
Africa (AFRO)	8.7/100 000
The Americas (PAHO)	73.5/100 000
Eastern Mediterranean (EMRO)	4.3/100 000
Europe (EURO)	91.5/100 000
South-east Asia (SEARO)	3.2/100 000
Western Pacific (WPRO)	11.8/100 000

It is significant that the median age of the world's population is increasing as a result of improved health care. With the emergence of prostate-specific antigen (PSA) screening, the proportion of cases of prostate cancer diagnosed has been increasing. Prostate cancer is one of the most prevalent malignancies affecting men in the developed world — the probability of a male in a western country dying of prostate cancer is approximately 3% [3].

According to the American Cancer Society, an estimated 217 730 new cases of prostate cancer occurred in the USA during 2010 [4]. Prostate cancer is the most frequently diagnosed cancer in men and more than 65% of all prostate cancer cases are diagnosed in men 65 years and older. Advanced age, benign prostatic hyperplasia, influence of hormones, a high fat diet, a positive family history, occupational hazards, sexual behaviour, race, STDs and tobacco usage are a few extensively researched risk factors for prostate cancer.

3. RADIOBIOLOGY

Nothing is as valuable to the radiation oncologist as a knowledge of radiobiology for various tumours. Prostate cancer offers several challenging issues ranging from the true value of the α/β ratio, the biological equivalence between external beam radiotherapy (EBRT) and brachytherapy, and the effect of relative biological effectiveness for permanent implantation with iodine-125 seeds or with hypofractionation [5].

Several randomized clinical trials have shown improved biochemical control rates in prostate cancer patients treated with doses of radiotherapy of more than 70 Gy using conventional fractionation, but a higher risk of late toxicity has been observed for patients treated in the high dose arms of these studies [6–11].

In order to reduce radiation induced toxicity, several strategies, such as the use of intensity modulated radiotherapy, high dose rate (HDR) brachytherapy and hypofractionation have been proposed [11–16].

Recently documented results have shown that prostate cancer has a low α/β ratio (0.8–2.2 Gy), which has significant therapeutic implications [17]. Treatment fractions higher than a standard 1.8–2 Gy fraction may be radiobiologically and therapeutically more effective. Therefore, hypofractionation (i.e. fractions of 2.5–3.5 Gy) has

been proposed and used in Australia, Canada and the United Kingdom in order to optimize the therapeutic ratio by taking into account the high sensitivity of prostate cancer to radiotherapy fractionation, as compared with nearby late responding tissues, such as the rectum, bladder and urethra [18, 19]. Moreover, delivering a higher dose in a reduced number of fractions may be convenient for patients, and logistically advantageous for busy radiotherapy departments, and at the same time, it reduces the cost of radiotherapy in 'pay per fraction' reimbursement systems.

The current evidence suggests that the differential fractionation sensitivity (tumour/normal tissue) favours the use of hypofractionated radiotherapy schedules for all risk groups of prostate cancers. This is also beneficial logistically, especially in a limited resource setting [17].

The α/β ratio for prostate cancer is indeed low when compared with other solid tumours, and alternative or more effective radiotherapy in the form of hypofractionation (EBRT or HDR brachytherapy) may be preferred in the radiotherapy management of localized prostate cancer.

Even with the increased late effects of high dose per fraction, there is still a potential for dose escalation beyond external radiotherapy limits using HDR brachytherapy. Radiobiological models support current clinical evidence for equivalent outcomes in localized prostate cancer with either low dose rate (LDR) or HDR brachytherapy using current dose regimens.

However, HDR brachytherapy dose escalation regimens might be able to achieve higher biologically effective doses of irradiation in comparison with LDR, and hence, improved outcomes. This advantage over LDR would be amplified should prostate cancer possess a high sensitivity to dose fractionation (i.e. a low α/β ratio), as current evidence suggests.

There is clinical evidence which suggests that prostate tumours contain a low proportion of proliferating cells and have a lower α/β ratio than the other epithelial tumours, in the range of 1.2–2.5 [20, 21], and it is suggested the value of 1.5 should be used for dose equivalence calculation for different treatment schedules.

4. PATIENT SELECTION AND RISK GROUP MANAGEMENT

The contemporary management of patients with clinically localized adenocarcinoma of the prostate should be guided by the risk–benefit ratio for the individual patient.

For patients with significant co-morbidity and low risk disease, the conservative approaches known as 'active surveillance' or 'watchful waiting' should be strongly considered. For these patients, the risk of dying of the prostate cancer (very low) when balanced against morbidity (almost certain) and the cost of therapy (very expensive) argues strongly for a conservative approach, even in countries with available resources.

In countries with limited healthcare resources, an even stronger argument can be made for conservative management. As the severity or extent of the disease increases, the evidence for intervention becomes more compelling and the degree of morbidity associated with treatment is increasingly justified by the benefits of therapy as reported by the results of phase III trials [22].

4.1. NATIONAL COMPREHENSIVE CANCER NETWORK RISK GROUPS AND PATIENT MANAGEMENT

For practical purposes, patients with localized prostate cancer are usually divided into three major groups: (1) low risk, (2) intermediate risk and (3) high risk of recurrence. (Additional subgroups may also be used.) Although numerous schemes have been proposed, the National Comprehensive Cancer Network (NCCN) guidelines have been most widely adopted in the United States of America (Table 2)[1] [23].

[1] Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2014.© 2014 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go on-line to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN content are trademarks owned by the National Comprehensive Cancer Network, Inc.

TABLE 2. NCCN RECURRENCE RISK STRATIFICATION VERSION 2.2014

Localization	Recurrence risk level	Indicators
Clinically localized	Very low	— Tumour stage T1c — Gleason score ≤6 — PSA <10 ng/mL — <3 prostate biopsy cores positive; ≤50% cancer in each core — PSA density <0.15 $ng \cdot mL^{-1} \cdot g^{-1}$
	Low	— T1–T2a — Gleason score 2–6 — PSA <10 ng/mL
	Intermediate	— T2b–T2c — Gleason score 7 or PSA 10–20 ng/mL
	High	— T3a or Gleason score 8–10 or PSA >20 ng/mL
Locally advanced	Very high	— T3b–T4
Metastatic		— Any T, N1 — Any T, any N, M1

Low risk patients: For patients who are considered low risk under this risk group classification scheme and who have an expected survival of <10 years, a conservative approach is usually favoured, such as watchful waiting or, in selected cases, EBRT using either 3-D conformal radiotherapy (CRT), intensity modulated radiotherapy (IMRT) or brachytherapy. For those who would otherwise have a life expectancy of ≥10 years, radiotherapy or radical prostatectomy are most commonly recommended, but in selected cases, expectant management is considered appropriate. Therapy for low risk patients is usually some form of limited monotherapy. This means that when radiotherapy is used, it is directed only at the prostate, and hormonal therapy is not recommended. Similarly, these low risk patients are generally spared a lymph node dissection. For low risk patients, neither bone scans, computed tomography (CT) scans, magnetic resonance imaging (MRI) or other staging studies are routinely indicated [24]. When EBRT is used, moderate dose escalation of 70–79 Gy seems justified and treatment should be limited to the prostate only [6, 7, 10, 25].

Intermediate risk patients: For patients with intermediate risk disease with a life expectancy of <10 years, conservative management remains a viable option, whereas for those with a life expectancy of more than 10 years, definitive local therapy (radical prostatectomy or radiotherapy) is usually recommended. Recommended therapy for intermediate risk patients may include a monotherapy, some form of radiotherapy alone, or a combined modality therapy, radiotherapy combined with short term (4–6 months) neoadjuvant (i.e. before radiotherapy) androgen deprivation therapy (ADT). Combined modality therapy may be indicated for those with two or more adverse features [26–29]. In addition, the radiation fields may be modified to include the pelvic lymph nodes in addition to the seminal vesicles depending on the perceived risk of regional disease [30]. For most of these patients, staging, which includes bone scans, CT scans, MRIs and other staging studies, is usually not indicated. An exception to this rule might include patients with multiple adverse features such as a patient with a PSA 11–19 and a Gleason score of 7 with bulk disease, or with approximately 50% of their core biopsies containing tumour. When EBRT is used, moderate dose escalation of 70–79 Gy is recommended [6, 7, 10, 25]. When indicated, the pelvic lymph nodes should be treated with 45–50 Gy [30]. Cone down boost to the prostate using some form of brachytherapy instead of EBRT is commonly used in the USA, but level I evidence is lacking. However, one trial supports the superiority of a brachytherapy boost when compared to conventional dose EBRT [9].

High risk patients: For patients at high risk, EBRT is usually more comprehensive (prostate, seminal vesicles and pelvic lymph nodes), and long term adjuvant ADT (2–3 years) is generally considered the standard of care [31–33]. Some patients with multiple adverse factors, as indicated above, who would otherwise be considered intermediate risk patients, should probably be managed as high risk patients [34]. When EBRT is used, moderate dose escalation of 70–79 Gy, or more, is recommended [6, 7, 10, 35]. Cone down boost to the prostate using some

form of HDR brachytherapy instead of EBRT is commonly used in the USA also for these patients, but again, level I evidence is lacking. Retrospective studies suggest that brachytherapy may be a more effective modality than EBRT in subsets of these patients, and a single trial supports the superiority of a brachytherapy boost when compared to conventional dose of EBRT, but long term ADT was not included [9].

4.1.1. Alternative methods of risk stratification

A number of other systems for stratifying patients have been developed but only a few are widely used. Kattan nomograms [36] have been made available on-line and are of interest because of their ease of use. Unfortunately they have not been used in clinical trials, and exactly how they should be used to direct therapy is unclear.

The risk groups suggested by the Radiation Therapy Oncology Group (RTOG) have been validated and can be applied for making treatment recommendations, but are not widely used.

A proposal has been made to modify the current American Joint Committee on Cancer's staging system to reflect the strengths of both the RTOG risk scheme and the NCCN guidelines, but such a change had not been adopted at the time of writing [37].

Alternatively, investigators have shown that building on the strengths of the Kattan nomogram for predicting the risk of distant metastases may be useful in predicting survival [38].

4.1.2. Key points for patient selection

The single most important factor for predicting the survival of prostate cancer patients is the Gleason score; accurate histopathological evaluation appears key to the optimal management of patients [39]. The clinical T stage is important but is limited by its lack of reproducibility [40]. These two factors, when combined with pre-treatment PSA, are predictive of outcome and are to be used to guide therapy [37].

5. RADIOTHERAPY TREATMENT APPROACH

The current standard of practice in prostate cancer is to combine all possible clinicopathological predictive factors to broadly stratify risk groups. These clinicopathological factors may suggest the likelihood of recurrence after radiation or surgery and the possible need for adjuvant therapies. Sophisticated prognostic tools include risk grouping, tables and nomograms, all of which use similar preoperative clinicopathological parameters: pre-treatment serum PSA, biopsy grade and volume parameters, and clinical tumour staging. The simplest of the most commonly used methods of risk stratification is the grouping developed by D'Amico et al. [41] which segregates patients diagnosed with prostate cancer into low, intermediate and high risk categories as described in Section 4.1.

The best management of localized prostate cancer has yet to be defined, but many published data show that surgery, radiotherapy, hormonal therapy and 'watchful waiting' can be used in isolation or in combination to treat the different risk groups for biochemical failure. Because of the use of PSA, up to two thirds of these men will be diagnosed with organ confined disease and a low to intermediate grade histological pattern, making these patients amenable to treatment with several potentially curative modalities that include radical prostatectomy and radiotherapy.

Radiotherapy represents one of the basic therapeutic methods in the treatment of localized disease, and an optimal irradiation dose is the cornerstone of a successful treatment in terms of local control of the disease, the overall survival of the patient, and acute and long term side-effects. Although the results of curative radiotherapy performed in the 1970s and 1980s, assessed with sequential PSA tests, have shown a higher than previously expected treatment failure rate with doses below 70 Gy, significant clinical data are available demonstrating that a significantly better outcome is seen as the dose to the prostate is increased [42–44].

5.1. EBRT DOSE ESCALATION

For intermediate and high risk disease, radical EBRT is standard, and there is increasing evidence for a dose response correlation for biochemical relapse free survival up to 86 Gy and beyond, a scenario possible with the advent of 3-D CRT and IMRT.

Several retrospective assessments of dose escalation in the late 1990s suggested a biochemical disease free survival benefit with doses >70 Gy [45–47].

Several randomized studies have confirmed this hypothesis since 2002 after releasing their preliminary results. Delivering a dose of 75–80 Gy definitively improved biochemical disease-free survival for both low and high risk patients, no matter which treatment technique was used (i.e. either LDR brachytherapy, non-3-D CRT or sophisticated proton therapy procedures) [8–10]. An improvement from 60–65% after 70 Gy and 70–80% after 78–80 Gy in 5 year year biochemical disease-free survival has been reported [10, 46].

Unfortunately, in these studies late toxicity was significantly worse for patients treated in the high dose arms in the rectum (patients treated with external radiotherapy) or in the bladder, urethra or both (in patients treated with a LDR brachytherapy boost) [9].

To search for an improved outcome with dose escalation but with reduced side-effects, several authors have tested doses above 80 Gy (or equivalent) as part of well-established pilot studies or phase II trials, using either IMRT [35, 48] or hypofractionated treatment protocols with HDR brachytherapy [13, 14].

5.2. DOSE ESCALATION WITH BRACHYTHERAPY BOOST

Brachytherapy may be used as a boost to the prostate in combination with EBRT in intermediate and high risk group patients. There are two competing modalities of brachytherapy, i.e. permanent LDR brachytherapy, with either ^{125}I or ^{103}Pd seeds, and temporary HDR brachytherapy with ^{192}Ir or ^{60}Co sources. Although the likelihood of a randomized clinical trial comparing LDR brachytherapy with HDR brachytherapy implants is unlikely, radiobiological modelling allows a better understanding of the available clinical data for these two forms of brachytherapy. Of course, the effect of patient selection bias cannot be completely avoided. HDR brachytherapy may provide an advantage from the radiobiological point of view. There is convincing evidence that prostate cancer may have a low α/β ratio, similar to that of late responding normal tissues (rectum, bladder), rendering it more sensitive to dose fractionation. HDR brachytherapy implants have the advantage of control over post-implant dosimetry by modulating the source dwell time and position, and the dose escalation can be safely achieved. This flexibility is not possible in LDR brachytherapy implants. On the other hand, HDR brachytherapy requires several sessions and a brief hospital stay.

Temporary brachytherapy using stepping source technology needs no special source preparation and causes no post-implant radiation protection problems. It also allows fractionated treatment schedules as well as individual dose optimization and high delivery quality assurance. The only disadvantage compared to LDR permanent seed implants is the need for fractionation, which results in a higher workload in the department. On the other hand, there may be some cost benefits in using HDR implants if the costs of LDR seeds, which are used once per patient, are compared with HDR treatments over a fixed time period. The radiation source and staffing costs of HDR treatments are stable, while the growing number of implanted seeds purchased for each patient continue to add up. This benefit would be applicable in departments with a high volume of implants.

The most common application of temporary brachytherapy in prostate cancer is its use as a local dose escalation method complementary to external beam techniques. This combination allows a lower normal tissue dose in the surrounding tissues and offers a very high local dose deposition to the prostate tumour. This treatment is indicated in intermediate or high risk cases without nodal involvement or metastases. Long term follow-up data confirm that HDR boost combined with external beam radiation results in excellent biochemical control rates [13, 14, 49–51]. In experienced hands, a 67–78% biochemical relapse-free rate is achievable with a genito-urinary/gastrointestinal (GU/GI) toxicity rate of 5–7% for >grade 3 complications. Usually, temporary brachytherapy causes the same level of erectile dysfunction as permanent or LDR seed implants — around 30–40%. Urethral strictures (approximately 8% G2 or higher) are the most common treatment related injuries following HDR prostate brachytherapy. Both clinical and dosimetry factors appear to influence the risk of stricture formation [52, 53].

The role of androgen deprivation in conjunction with brachytherapy is notable. The role of combining neoadjuvant androgen deprivation (NAAD) and permanent prostate brachytherapy is to reduce the prostate size for optimal implantation. Ebara et al. showed that a three month course of neoadjuvant Luteinizing-hormone-releasing hormone (LHRH) agonist induced sufficient volume reduction effectiveness for a large prostate volume (a reduction of 32–35%) [54].

5.2.1. Permanent implants with low dose rate seeds

Over the last 15 years, there has been a dramatic increase in the utilization of permanent seed implants for early disease prostate carcinoma in developed countries because of the convenience and availability of isotopes. Permanent interstitial brachytherapy with ^{125}I or ^{103}Pd seeds is a well-established approach as a single modality treatment for low risk prostate cancer, and over 44 000 procedures were performed in 2000 [55]. It may also be used as a boost in conjunction with EBRT.

The local control reported by several centres nationally and internationally has been excellent. These treatments are very popular among patients and urologic surgeons for reasons of logistics and convenience, and they have therefore been driving this technology over the last few years.

Urinary tract frequency, urgency and, less commonly, urinary retention are seen in most patients but subside with time. Rectal ulceration may also be seen. In one series, a 10% 2 year actuarial genito-urinary grade 2 complication rate and a 12% risk of rectal ulceration were seen [56, 57]. LDR brachytherapy has the advantage of being a one-time procedure and the existing long term follow-up supports its excellent outcome and low morbidity [58, 59]. However, it has the disadvantage of a limited capability of adequate dose coverage beyond the prostate and anatomical restrictions such as pubic arch interference. Furthermore, in low income or low resource settings, the use of ^{125}I and ^{103}Pd seeds is not convenient as they have to be imported and raise radiation protection and security issues.

5.2.2. Dose escalation using external beam radiation therapy plus high dose rate brachytherapy

Several retrospective studies with more than 5 year follow-up have described the outcome of patients treated with combination of EBRT and HDR brachytherapy boost [14, 53, 60–65], but data from prospective randomized trials comparing results of this combination with dose escalation 3-D CRT or IMRT are lacking. Data from Hoskins et al. [66] support this approach to dose escalation in a phase III randomized trial, which reports a significant improvement in actuarial biochemical relapse free survival in favour of the combined brachytherapy schedule ($p = 0.03$). The patients received 55 Gy in 20 fractions over 4 weeks or a combined schedule of 35.75 Gy in 13 fractions over 2.5 weeks' EBRT followed by HDR brachytherapy (17 Gy in 2 fractions over 24 hours). Patients randomized to brachytherapy had a significantly better FACT-P (Functional Assessment of Cancer Therapy — Prostate) score at 12 weeks ($p = 0.02$). Furthermore, they showed less rectal toxicity and an improved quality of life under the combined treatment that included a brachytherapy boost. Dose escalation is therefore feasible by combining EBRT with HDR brachytherapy and provides optimal intensity modulated conformal radiation dose delivery.

Recently, a study by Tang et al. [67] evaluated the results of 88 patients treated with EBRT alone (66 Gy) and EBRT (46 Gy) combined with HDR brachytherapy (16–20 Gy). For the HDR brachytherapy cohort, the overall actuarial 5 year biochemical control was 67.4%. They noted a significant advantage ($p = 0.011$) when biological equivalent dose calculations were used to compare results of HDR brachytherapy combined with EBRT. They have also compared the results in terms of HDR brachytherapy total dose, 16 Gy versus 20 Gy, observing that the 5 year biochemical control rates, using the RTOG-ASTRO Phoenix definition (issued by the Radiation Therapy Oncology Group and the American Society for Therapeutic Radiology and Oncology) were 58.8% and 77.3%, respectively ($p = 0.07$). Galalae et al. [49] investigated long term outcome by risk group using HDR brachytherapy and EBRT with or without neoadjuvant androgen deprivation. The 611 patients were grouped as follows: 46 low risk patients, 188 intermediate risk patients and 359 high risk patients. Using the ASTRO definition for biochemical failure, they observed that the actuarial biochemical cure and disease-free survival rates at 5 years and 10 years were 77% and 67%, and 73% and 49%, respectively. For the different risk groups, the actuarial 5 year biochemical control rates were 96% for the low risk group, 88% for the intermediate risk group and 69% for the high risk group. They observed that Gleason score and grade were statistically significant predictive factors of biochemical control.

They also observed that clinical stage and initial PSA were also statistically significant predictive factors for biochemical control.

Deger et al. [50] evaluated 422 patients with localized prostate cancer treated between 1992 and 2001 with HDR brachytherapy and 3-D radiotherapy. All patients underwent laparoscopic pelvic lymph node dissection to exclude patients with lymphatic involvement. The biochemical failure was also defined according to the ASTRO criteria. Biochemical control according to stage was 100% for T1, 75% for T2 and 60% for T3 at 5 years. Five year biochemical control was 81% in the low risk group, 65% in the intermediate risk group and 59% in the high risk group. Five year overall survival and biochemical control were 87% and 94%, respectively. The researchers also observed that initial PSA, risk group and age were significantly related to biochemical control.

A limited number of papers have published the results of HDR brachytherapy and EBRT for prostate cancer using the RTOG-ASTRO Phoenix definition. This definition states: "To avoid the artifacts resulting from short follow-up, the reported date of control should be listed as 2 years short of the median follow-up" [68].

Chin et al. [69] published the results of 65 consecutive patients treated between 1998 and 2004 with a combination of EBRT and HDR brachytherapy given in 2 fractions. Sixty patients (92.3%) in the study were considered intermediate or high risk. With a median follow-up of 3.5 years (0.6–5.8), the results showed that 2 patients had died of metastatic disease and 4 other patients had biochemical failure, giving a 3 year actuarial biochemical control rate of 90.8%.

Yamada et al. [70] also reported the results of 105 patients consecutively treated between 1998 and 2004 with EBRT (45–50.4 Gy) and HDR brachytherapy (5.5–7.0 Gy per fraction). With a median follow-up of 44 months (8–79 months), the actuarial 5 year biochemical control rates for low, intermediate and high risk groups were 100%, 98% and 92%, respectively.

Vargas et al. [71] performed a matched pair analysis of patients treated with combined EBRT and HDR brachytherapy from January 1993 to March 2003. A total of 1432 patients were evaluated. There were 755 cases identified as having a risk of positive pelvic lymph nodes of greater than 15% using the Roach formula. Of these, 255 cases were treated without pelvic EBRT and randomly matched by Gleason score, clinical stage and initial PSA to 500 cases treated with pelvic EBRT, resulting in 250 pairs. As a result, they observed that biochemical failure and overall survival was not significantly different for patients treated with pelvic radiotherapy. At a median follow-up of 4 years, the biochemical control and overall survival rates were 78%, 86%, 89% and 88%, respectively.

Patients considered high risk have a higher chance of biochemical failure. This phenomenon could be a consequence of current inadequate imaging of lymph node or bone metastasis or due to subclinical metastatic spread that remains undetectable during radical treatment. However, tumour biology itself could lead to the progression of the disease in the high risk group. As a consequence, risk adapted therapy is very important in these cases. The combination of EBRT and HDR brachytherapy is an alternative strategy of dose escalation that can potentially achieve an even higher biological equivalent dose to the tumour when comparing 3-D radiotherapy or IMRT, but for patients in the high risk group, the localized dose given by HDR brachytherapy may be a potential disadvantage, because a microscopic spread outside the prostate and even outside its capsule may occur. In these cases, the combination of HDR brachytherapy and EBRT can provide treatment to potential areas of microscopic spread. The as yet unanswered question is whether adding pelvic lymph node radiation, instead of the more localized EBRT, to HDR brachytherapy in prostate cancer patients who have a high risk of positive lymph nodes (more than 15%) will improve the outcome, and this question is still controversial in the literature [72].

5.3. BRACHYTHERAPY AS MONOTHERAPY

Prostate brachytherapy as a single modality is generally reserved for patients with clinically confined prostate cancer. A brachytherapy boost with supplemental EBRT has primarily been used in patients who are not in the low risk category and its use is based on the risk group. Biochemical disease free survival rates for radical prostatectomy versus transperineal ultrasound guided prostate implant for patients with early prostate cancer were evaluated, and the 5 year biochemical disease-free survival rates for radical prostatectomy versus implant were nearly identical for the favourable group (93% versus 92%), intermediate group (70% versus 70%) and poor group (50% versus 52%) patients [73].

5.3.1. High dose rate brachytherapy as a monotherapy

HDR fractionated monotherapy of prostate cancer was introduced by Yoshioka et al. [74]. Later feasibility studies were published by Martinez et al. [63] and Martin et al. [75] in the early 2000s. Monotherapy is used in a similar way to low dose rated seed implantations: the target population are men with low risk prostate cancer. With regard to fractionation, some groups use 3–4 separate implants while others use 2 implants that deliver 3–4 fractions. The fraction dose varies between 8.0–9.6 Gy to the peripheral zone. The interfraction interval is a minimum of 6 hours. There are no published phase III clinical investigations comparing HDR monotherapy with other radiotherapy modalities. Available phase II studies suggest an excellent biochemical response with no differences seen in acute and late toxicity between dose schemes of 34 Gy/4 Fx, 36 Gy/4 Fx or 31.5 Gy/3 Fx [76].

Groups who have collected data over a number of years report a 5 year biochemical control rates of 91% (Phoenix definition, nadir+2ng/ml) and local control rates of 98.9% [77].

A recent update of HDR prostate monotherapy experience at William Beaumont Hospital (WBH) and California Endocurietherapy Center (CET) involving 248 patients treated between July 1993 and December 2004 [78, 79]. The 171 patients at WBH and 77 patients at CET treated with HDR monotherapy were compared with a group of 206 patients treated at WBH with permanent seeds using palladium-103. The hypothesis tested for the phase II study was that, owing to the radiobiological and physical dose distribution advantages, intensity modulated HDR prostate monotherapy should be less toxic than permanent seed brachytherapy while maintaining similar biochemical control rates. At WBH, a schedule of 9.5 Gy × 4 had a dose equivalence of EBRT of 75.6 Gy (42 fractions of 1.8 Gy), and at CET, the 7 Gy × 6 in two implants, the second performed one week after the first, had an equivalent EBRT dose of up to 76 Gy (38 fractions of 2 Gy). When HDR outcomes were compared to the LDR brachytherapy patient outcomes during the same time period, 5 year biochemical control rates were similar for both HDR and LDR monotherapy. However, HDR brachytherapy was associated with less acute and less chronic genito-urinary and gastrointestinal toxicities. The five year Phoenix biochemical control (BC) was 91%, and 88% for HDR at WBH and HDR at CET, respectively. HDR was associated with less acute grade 1–3 dysuria — 60% versus 39% ($p < 0.001$), urinary frequency/urgency — 90% to 58% ($p < 0.001$), and rectal pain — 17% to 6.5% ($p < 0.001$), as compared to LDR implants performed during the same time period. Long term urinary frequency/urgency was 54% versus 43%, ($p = 0.03$) and dysuria (22% versus 15%) was less with HDR. The 5 year actuarial impotence rate was 30% for LDR and 20% for HDR ($p = 0.23$).

Regarding toxicity, the incidence of brachytherapy related normal tissue injury could be minimized by using strict rectal dose constraints (V40 < 8cc and D5cc > 27 Gy) as well as keeping the volume of high dose areas low [74]. Rigorous quality assurance practices [80] can avoid unplanned dosimetry changes between different fractions using the same implant:

— Theoretical advantages of brachytherapy in form of temporary implantations include: Potential for a boost-in-boost radiation due to the steep dose fall-off of the source in the peripheral zone, which is the most common target location;
— Shorter learning curve compared to LDR implantations;
— No movement of the source in relation to the target volume within the time of radiation;
— More effective dose–volume optimization possible with stepping source technology;
— Potential for lower toxicity owing to the improved protection of risk areas such as the urethra, rectum and bladder base, as well as the bulbous penis.

There are some disadvantages compared with seed implant which are discussed in the literature:

— Fractionation with one implant can change the needle to target relationship compared with the initial situation. Therefore, a high level of quality assurance is needed before each application of radiation.
— Lack of comparative and prospective randomized quality of life studies.
— Unclear cost compared to LDR treatments, however, in high workload centres, HDR monotherapy could represent an economic advantage.

5.4. POST-OPERATIVE RADIOTHERAPY IN LOCALIZED PROSTATE CANCER: THE ROLE OF ADJUVANT AND SALVAGE RADIOTHERAPY

Support for the role of post-operative EBRT following radical prostatectomy has grown over the last few years with the completion of several phase III randomized trials and a host of retrospective data [81–88]. This review summarizes selected studies providing support for postoperative radiotherapy, and provides recommendations for when and how adjuvant and salvage therapy should be administered.

Biochemical failures are common post-prostatectomy and are frequently due to local disease. Following a radical prostatectomy, a significant number of patients will experience biochemical recurrence. This can be an early or a relatively late event. For example, Pound et al. found that 25% of patients with recurring disease experienced a recurrence after 5 years [87]. Long term studies show that biochemical failures continue to occur beyond 10 years, with this relatively common event occurring more frequently in patients with one or more adverse features. For example, among 1688 patients with a Gleason score of 7 undergoing radical prostatectomy at the Mayo Clinic, >50% (i.e. 52% of patients with a Gleason score of 3 + 4, and 62% with a Gleason score of 4 + 3) experienced biochemical failure within 10 years with no evidence of a plateau noted [88]. These late biochemical failures suggest that many of these patients have persistent microscopic disease following radical prostatectomy that continues to grow slowly over a number of years. Support for this hypothesis is found in the relatively high response rates when salvage radiotherapy is administered [89–91].

5.4.1. Definitions of biochemical failures post-prostatectomy

Definitions for biochemical failure following radical prostatectomy have evolved over the past 15 years. Some studies have defined biochemical failure as a PSA greater than 0.6 ng/mL (Washington University, St. Louis) [92]. Others, such as Stein et al., use a cut-off of greater than 0.4 ng/ml, while investigators from Johns Hopkins have chosen to use a definition of greater than 0.2 ng/ml [93, 94]. Ultra-sensitive PSA determinations are clearly more sensitive and work performed at Stanford and other institutions have demonstrated that PSAs can be detected up to three years earlier when ultra-sensitive assays are used than when conventional assays are used [95, 96]. At UCSF (University of California, San Francisco), the use of ultra-sensitive assays is favoured.

Nevertheless, there is no consensus as to the preferred definition of biochemical failure among urologists. Amling et al. evaluated a number of definitions: greater than 0.2, greater than 0.3, greater than 0.4 and greater than 0.5, and concluded that greater than 0.4 was the preferred definition [97]. Regardless of the PSA definition used, additional patients continue to fail beyond 10 years. Given the recent evidence supporting the value of early compared to delayed radiotherapy, a lower threshold for post-operative radiotherapy seems prudent [81–85]. The lack of consistency as to the definition of biochemical failure has resulted in some confusion in the interpretation of the available literature regarding adjuvant (immediately after radiation and prior to any evidence of recurrence) versus salvage (treatment for a documented recurrence) radiotherapy. It is important to note that earlier assays only detected PSAs greater than 0.3 ng/mL and thus, many of the patients who were assumed to be receiving adjuvant radiotherapy may in fact have had persistent disease. If more recent studies include patients whose PSAs were undetectable with ultra-sensitive assays, we can be sure that these patients received true adjuvant therapy and may therefore have had a more favourable outcome.

5.4.2. Evidence for adjuvant radiotherapy

A number of retrospective studies support adjuvant radiotherapy, e.g. Quinn et al. [98] compared patients with multiple positive margins who received adjuvant radiotherapy with those who did not, and demonstrated a dramatic improvement in biochemical control rate. Data from Catalona and Smith also demonstrated that immediate radiation in patients with adverse pathologic features was associated with an improvement in biochemical control [99]. Most recently, investigators from Johns Hopkins showed that there was an increase in prostate-cancer specific and overall survival associated with salvage radiotherapy in men with a prostate-specific antigen doubling time of less than 6 months, after adjustment for pathological stage and other established prognostic factors. They noted that salvage radiotherapy initiated more than 2 years after recurrence, or in men whose prostate-specific antigen level never became undetectable, provided no significant increase in prostate cancer specific survival [91].

More compelling evidence for the value of adjuvant radiotherapy can be found in three recent phase III randomized trials [81–83]. SWOG (formerly known as the Southwest Oncology Group) set out to determine whether adjuvant radiotherapy improves metastasis free survival in patients with stage pT3 N0 M0 prostate cancer. Patients (n = 425) were randomly assigned to receive either 60–64 Gy of EBRT delivered to the prostatic fossa or usual care plus observation. The primary outcome monitored was metastasis free survival, defined as the time to the first occurrence of metastatic disease or death due to any cause, and secondary outcomes included prostate-specific antigen (PSA) relapse, recurrence free survival, overall survival, lack of need for hormonal therapy and post-operative complications. In the initial report, 36% of men in the adjuvant radiotherapy group were diagnosed with metastatic disease or died compared with 43 % in the observation group (hazard ratio: 0.75; 95% confidence interval (CI), 0.55–1.02; p = 0.06). The median PSA relapse free survival was 10.3 years for radiotherapy vs 3.1 years for observation (hazard ratio: 0.43; 95% CI, 0.31–0.58; p < 0.001), and the median recurrence free survival, was 13.8 years for radiotherapy vs 9.9 years for observation (hazard ratio: 0.62; 95% CI, 0.46–0.82; p = 0.001). Although adverse effects were more common with radiotherapy that with observation in the updated analysis by 5 years, there were no differences in health related quality of life, and there may very well be an overall survival advantage in favour of adjuvant radiotherapy [100]. A subset analysis from this study suggests that earlier treatment is better than delayed treatment [101].

The European Organisation for Research and Treatment of Cancer (EORTC) have also confirmed the value of adjuvant radiotherapy in a larger study demonstrating a dramatic reduction in the rate of biochemical failure as well as time to clinical progression [82]. Patients eligible for this study had pN0 M0 tumours and one or more pathological risk factors including: capsule perforation, positive surgical margins and invasion of seminal vesicles. After a median follow-up of 5 years, biochemical and clinical progression free survivals were significantly improved in the irradiated group (p < 0.0001 and p = 0.0009, respectively). The rate of local regional failure was also lower in the irradiated group and severe toxicity (grade 3 or higher) was similar, with a 5 year rate of 2.6% vs 4.2% in the post-operative irradiation group, p = 0.07. More recently, a German series confirms the benefits of the role of adjuvant radiotherapy with a low incidence of late complications from radiotherapy [83]. These studies taken as a group demonstrate that patients with adverse prognostic features, including pT3 disease or positive margins, should receive adjuvant radiotherapy. With modern techniques, it is expected that the small risk of late complications could be reduced.

5.4.3. Salvage radiotherapy

Salvage radiotherapy is the only curative option for patients experiencing biochemical failure after radical prostatectomy, and a growing body of data suggests earlier intervention is better than delayed intervention [86, 91]. From a multi-institutional database of 2299 patients undergoing post-operative radiotherapy, a matched pair analysis was performed with patients with pT3-4N0 who received either salvage radiotherapy or early adjuvant radiotherapy. In total, 211 patients receiving early adjuvant radiotherapy and 238 patients receiving salvage radiotherapy were matched in a 1:1 ratio, according to preoperative prostate-specific antigen Gleason score, seminal vesicle invasion, surgical margin status and follow-up from date of surgery. The authors concluded that early adjuvant radiotherapy for pT3-4N0 prostate cancer significantly reduces the risk of long term biochemical progression after radical prostatectomy compared with salvage radiotherapy.

A number of investigators have attempted to develop models to predict the likelihood of successful salvage radiation. Stephenson et al. [102] reported on 1540 patients who underwent salvage radiation. They used a multivariable Cox regression analysis to construct a model to predict the probability of disease progression after salvage radiotherapy. They developed a nomogram that included PSA level before salvage radiotherapy (p < 0.001), prostatectomy Gleason grade (p < 0.001), PSA doubling time (p < 0.001), surgical margins (p < 0.001), ADT before or during salvage radiotherapy (p < 0.001), and lymph node metastasis (p = 0.019). This analysis is of interest because it provides evidence that even patients with seemingly very unfavourable disease may do relatively well if offered salvage therapy. For example, 27% of patients with a Gleason score of 8 to 10 were estimated to have 4 years of biochemical control (if their PSA at the time of radiation was less than 2 ng/ml). If their margins were positive, the 4 year control goes up to 35%. Their control rate jumps up to 50% if their doubling time exceeds 10 months [102]. This type of modelling has been instrumental in advising patients as to their prognosis and also in providing recommendations for treatment. The model used in this trial demonstrated that the use of neoadjvant hormone therapy might improve the observed control rate. This collection of phase III randomized trials and

retrospective studies discussed in this section have provided a large and compelling body of evidence to suggest that adjuvant radiotherapy should be considered the gold standard for post-prostatectomy patients with adverse pathologic features. These data also suggest that radiotherapy is an effective salvage approach in patients who fail after radical prostatectomy.

5.4.4. Pelvic radiotherapy in post-operative patients

Additional questions that need to be answered include how patients should be treated when they undergo EBRT. A number of studies suggest that neoadjuvant ADT should be added to salvage radiotherapy in a fashion analogous to neoadjuvant ADT in patients with locally advanced disease [29, 90, 102, 103]. For example, in a retrospective analysis of patients treated at Memorial Sloan Kettering Cancer Center, Katz et al. demonstrated that patients with multiple adverse features had a better biochemical control rate when neoadjuvant ADT was added to EBRT. Similar data have been reported from MD Anderson Cancer Center [103].

An additional consideration in the management of patients failing after radical prostatectomy includes whether they should receive whole pelvic radiotherapy. Retrospective data reported by investigators from Stanford suggest that such patients with adverse features have an improved biochemical control rate with the addition of whole pelvic radiation compared to prostate bed only radiation, a control rate of 53% compared with 36%; $p = 0.033$ [104]. The RTOG is currently running a 3 armed phase III trial (RTOG 0534) comparing radiation therapy only to the prostate, radiation with hormone therapy, and radiation with hormone therapy and whole pelvic radiotherapy to answer this question.

An additional consideration in the management of patients in the post-operative setting is the fact that set-up error and organ (target) movement problems have been shown to often compromise the accuracy of radiotherapy. Work from UCSF has shown that up to 30 to 40 per cent of treatments would be inaccurate by >5 mm if no corrective measures were taken [105]. Thus, a number of institutions have adopted the use of on-line imaging, using gold markers for the anastomosis to guide the salvage approach. The role of dose escalation in the salvage setting remains to be determined.

5.4.5. Final conclusions on post-operative radiotherapy

Compelling phase III trials have provided level I evidence that adjuvant radiotherapy should be the treatment of choice in patients with adverse pathologic features after radical prostatectomy. Salvage radiation is the only known curative modality for patients failing biochemically after radical prostatectomy. The role of dose escalation, on-line imaging, neoadjuvant hormone therapy and whole pelvic radiotherapy are being studied in a number of institutions, but only phase III randomized trials will answer these questions definitively.

5.4.6. Hypofractionation

The α/β ratio is important in determining the equivalence of different radiation fractionation schemes and biological equivalent dose through the formula ($nd[1 + d/\{\alpha/\beta\}]$), along with the number of fractions (n) and fraction size (d). The shape of the radiation dose–response curve follows the linear–quadratic model, where α is estimated from the linear component and β from the quadratic component. Thus, the α/β ratio can serve as a measure of the sensitivity of the irradiated tissue to radiation fraction size. Late responding normal tissues generally have a low α/β ratio and are thus more sensitive to large fraction size than early responding normal tissues or tumours, which generally have a high α/β ratio. Tumours generally have α/β ratios of 8 or more, while ratios of 3 or less are seen in late responding normal tissues. Thus, in an attempt to enhance the therapeutic ratio, smaller fraction sizes of 1.8–2 Gy are used in conventional fractionation to lessen the effect on late responding normal tissues.

Of interest is that analyses of prostate cancer tumour control in available clinical datasets [15–17, 106] have suggested an α/β value of approximately 1.4–3 [107], although a wider range between 0.52–8.4 has also been reported [108]. The generally accepted prostate tumour α/β ratio of 1.4–3 is lower than most typical tumours. This is also lower than the α/β value for the rectum [109], since both animal studies [110–114] and clinical results [115–117] suggest an α/β ratio of >4 Gy for late rectal sequelæ. Thus, increasing the dose per fraction, through hypofractionation regimens, may lead to a greater radiation effect on the prostate cancer relative to the normal tissue (e.g. rectum).

Several phase I/II and phase III trials have investigated the role of hypofractionation in the radiation therapy of prostate cancer. Of the non-randomized trials, the Cleveland Clinic [118] reported one of the earliest phase I/II studies using IMRT in a hypofractionated schedule with ultrasound image guidance. The acute urinary toxicity rate for toxicity grades 2 and 3 was 18% and 1%, respectively. The acute grade 2 rectal toxicity rate was 9%, but no grade 3 acute rectal toxicity was seen. Late rectal toxicity was 4.5% for grades 2–4. The freedom from biochemical recurrence was similar to that in patients treated with conventional fractionation at the Cleveland Clinic (78 Gy at 2 Gy/fraction) during the same time period. Other non-randomized studies had similar findings and reported on well tolerated, varied hypofractionation regimens. The increase in side-effects seen was mainly in acute radiation side-effects. In a multi-institutional phase I/II study performed in Europe [119], acute grade 2 GI and GU toxicities were 36% and 44%, respectively. No grade 3 or 4 acute toxicity was seen. When compared to historical controls treated with conventional fractionation, the hypofractionation group experienced significantly greater toxicity of grade 2 or less that subsided within 2 months.

Hypofractionation clinical trials performed by the National Institute of Radiological Sciences [120] used carbon ion therapy in prostate treatment. The optimal hypofractionation dose was determined to be 3.3 Gy equivalent, to a total dose of 66 Gy equivalent. Overall 5 year freedom from biochemical recurrence rate was 83% with late grade 2 genito-urinary and gastrointestinal toxicities of 6% and 1%, respectively, and no grade 3 or higher toxicities. Patients at the Princess Margaret Hospital [121] had no acute grade 3 toxicity. Acute grade 2 GI and GU toxicity was reported in 11% and 25% of men, respectively. With regard to late toxicity, less than 5% of patients developed grade 2 GI and/or GU toxicity, and no grade 3, 4 or 5 toxicity was reported. The freedom from biochemical recurrence at 2.5 years was 82%. A US multi-institutional trial [122] of 110 patients treated with image guided IMRT to a total dose of 64.68 Gy in 2.94 Gy fractions reported grade 2 rectal bleeding of 12% with no grade 3 rectal toxicity. No late GU toxicity was observed. The median follow-up was 20 months.

The randomized trials varied in both dose per fraction and whether the arms received biologically equivalent doses. The increase in acute effects in the non-randomized studies was seen here as well. For example, a Canadian randomized trial [18] included 936 patients treated in two arms. No attempt was made to achieve biologically equivalent doses in both arms using the α/β ratio. At 5 years, the biochemical/clinical failure rate was higher in the hypofractionated arm compared with the conventionally fractionated arm. There was no difference in overall survival. Acute GU toxicity was higher in the hypofractionated arm but there were no statistically significant differences in late toxicity between the two arms. The incidence of late grade 3 or higher GU or GI toxicity was 1% and 2%, respectively. On the other hand, Yeoh et al. [19] randomized patients to either conventional fractionation or hypofractionation. Acute rectal toxicity at 1 month was worse in the hypofractionated arm and adversely affected daily activities. Late gastrointestinal and genito-urinary toxicity did not differ between the two dose schedules other than in regard to urgency of defecation. The overall survival rate free from biochemical recurrence was not significantly different between the two arms (55.9% and 85.3% at 5 years, respectively).

Some of the randomized trials that compared conventional fractionation and hypofractionation regimens were limited by the use of a conventional treatment dose that was too low or that was not biologically equivalent to the hypofractionation arm. This made the interpretation of these trials difficult.

However, the trial from the NCI Italy assumed an α/β ratio of 1.5 Gy for prostate tumour and 3.0 Gy for late responding normal tissue and attempted to attain biological equivalence between the two arms. The incidence of late rectal and urinary toxicity > grade 2 was not significantly different between the two fractionation schedules, with a significantly higher freedom from biochemical failure rate in the hypofractionation arm.

Some of the studies which have been completed or are ongoing [18, 19, 119–129] are shown in Table 3 [130]. In conclusion, outcomes and toxicity in prostate cancer patients treated in phase I–II trials with equivalent hypofractionated regimens have a low toxicity of 6–9% for G2 rectal toxicity [48, 119]. Randomized trials available in the literature showed no significant differences in late toxicity, with some showing evidence of improved outcomes with hypofractionation [18, 19, 123].

TABLE 3. FRACTIONATION SCHEDULES USED IN TRIALS

Total dose	Dose per fraction	Number of fractions	Number of patients	Site
50 Gy	3.13 Gy	16	705	Christie hospital, UK [124]
69 Gy	3 Gy	23	52	Gunma, Japan [125]
66 GyE	3.3 GyE	20	201	NIRS, Japan [120]
52.5 Gy	2.625 Gy	20	300	Edinburgh [119]
56 Gy	3.5 Gy	16	36	Jette, Belgium [119]
60 Gy	3 Gy	20	92	Princess Margaret [126]
70 Gy	2.5 Gy	28	770	Cleveland Clinic [127]
64.7 Gy	2.94 Gy	22	100	Multi-institutional trial [122]
58.1 Gy	3.63 Gy	16	100	
51.6 Gy	4.3 Gy	12	58 (ongoing)	
52.5	2.625 Gy	20	466	NCI, Canada [18]
66 Gy	2 Gy	33	470	
55 Gy	2.75 Gy	20	108	Adelaide [19]
64 Gy	2 Gy	32	109	
70.2 Gy	2.7 Gy	26	150	FCCC [128]
76 Gy	2 Gy	38	150	
62 Gy	3.1 Gy	20	83	NCI, Italy [123]
80 Gy	2 Gy	40	85	
70 Gy	2.5 Gy	28	Ongoing	RTOG 0415
73.8 Gy	1.8 Gy	41		
57 Gy	3 Gy	19	Ongoing	MRC [129]
60 Gy	3 Gy	20		

6. RADIATION DOSES AND TECHNIQUES

6.1. PRIMARY TREATMENT WITH EXTERNAL BEAM RADIOTHERAPY

6.1.1. Target volume definition

In order to define an appropriate clinical target volume (CTV) to treat prostate cancer with EBRT, the tumour growth pattern has to first be taken into consideration. Although the whole prostate gland is typically regarded as the main treatment target, the potential for extra-capsular extension (ECE, i.e. extension into fat surrounding the prostate), seminal vesicle invasion (SVI) and lymph node involvement (LNI) must be recognized when defining the CTV. The Partin tables were the first nomograms developed that allowed the making of predictions of the risk that a patient had ECE or SVI, and/or LNI based on their baseline pre-treatment PSA, clinical stage and Gleason score [131].

Recent studies have called into question the accuracy of the Partin tables because an extended lymph node dissection was not performed in the research on which they were based, and consequently not all of the relevant sites for nodal drainage were sampled and the total number of nodes may have been inadequate [132–134]. In addition, there may have been a higher false negative rate than generally recognized because standard histocytopathologic evaluations of lymph nodes appear to be less sensitive than they may have been with molecular and cytological assays [135–137].

D'Amico et al. [138] assessed the correlation between the percentage of positive biopsy cores and the clinical outcome in 421 patients with low or favourable intermediate risk prostate cancer patients. They observed that prostate cancer specific mortality was significantly higher in patients with ≥50% positive biopsies at diagnosis compared to those with <50% positive biopsies. Furthermore, Lieberfarb et al. observed in 2099 patients treated with radical prostatectomy that low risk patients with ≤50% positive biopsies and intermediate risk patients with ≤17% of positive biopsies had a low probability of ECE or SVI, and a concurrent 5 year bNED of ≥90%. Therefore they recommended considering the prostate only, without the seminal vesicles, when defining the CTV for patients undergoing radiotherapy [139].

Wheeler et al. completed a pathological study of organ specimens in 688 patients treated with radical prostatectomy and reported that the degree of radial ECE was proportionally associated with an increased risk of SVI and lymph node metastases [140]. Indeed, all 138 patients without capsular invasion showed neither SVI nor lymph node metastases regardless of Gleason score or tumour volume. ECE was also correlated with a marked reduction in progression free probability.

Perineural invasion and ECE are frequently simultaneous events. The pathologic feature of perineural invasion was significantly correlated with the 5 year PSA failure free survival rate in 381 patients treated with EBRT in a study by Beard et al. [141]. They also observed perineural invasion to be correlated with a positive biopsy and Gleason score of ≥8. Thus, if perineural invasion (and ECE) is found in the biopsy material, they recommend the inclusion of the seminal vesicles in the CTV, as well as the regional lymph nodes if additional unfavourable risk factors are present.

The degree of extraprostatic extension of the cancer should be taken into account when defining the CTV. The largest study evaluating the radial distance of ECE was performed on 712 prostatectomy patients by Teh et al. [142]. They found focal ECE, ECE <2 mm, ECE 2–5 mm, and ECE >5 mm in 38.1%, 19.1%, 36.1% and 6.7%, respectively. There was a significant correlation between the degree of ECE and rising clinical stage, pre-treatment PSA levels and Gleason score in the pre-treatment biopsy. Furthermore, focal and extensive extraprostatic extension was associated with a proportionally increased risk of SVI, lymph node involvement and a lower progression free survival. These results imply that for patients with intermediate and high risk prostate cancer, an additional margin of 5 mm of periprostatic tissue should be considered in order to include all the potential local tumour extension in the CTV.

Kestin et al. reported on patient risk status and the probability of SVI focusing specifically on the length of SVI [143]. A 1% risk of SVI for low risk patients (<T2b, Gleason < 7, PSA < 10 ng/ml) was reported. If one, two or all three factors happen to be higher, the SVI risk increased to 15%, 38% and 58%, respectively. Only 1% of the whole group of patients had a risk of SVI beyond 2 cm. The results from this study may be helpful to establish guidelines on whether to include seminal vesicles in the CTV and the volume of seminal vesicle to be

included. Inclusion of up to 2 cm of the SV for high risk patients and up to 1 cm for intermediate risk patients is recommended. For low risk patients, the inclusion of SV may not be necessary.

The treatment of pelvic lymph nodes is a controversial matter as the existing arguments in the literature supporting such treatment are inconclusive [144, 145]. The RTOG 7706 trial randomized 445 T1 and T2 patients in two arms between 65 Gy to the prostate and seminal vesicles versus 45 Gy to the pelvis with a final 20 Gy boost to the prostate and seminal vesicles [146]. No significant difference in 12 year overall survival was observed between the two treatment arms (i.e. 70% for patients treated exclusively to the primary tumour bearing organ versus 72% for patients treated to the pelvis). However, this study only included patients who were considered to be at low risk for lymph node involvement and preceded the availability of PSA.

More recently, RTOG 9413 (assessing the role of pelvic irradiation and the timing of hormone deprivation, either neoadjuvant concomitant or adjuvant for patients with a nodal risk >15%) demonstrated that there was improvement in progression free survival (the primary end point of the study) for those patients treated in the pelvic region. At the last follow-up, too few deaths from prostate cancer had occurred to be able address the issue of overall or cause-specific survival, but the trends tend to favour whole pelvis radiotherapy as superior to the other 3 arms [147, 148]. To date, every major phase III trial using long term ADT in high risk patients has included whole pelvic radiotherapy [31–33]. Thus, radiation oncologists may consider including or excluding pelvic lymph node region as part of treatment (with or without hormonal therapy) based on the risk of lymph node involvement, and take into account the risk of toxicity from existing comorbidities such as old age, diabetes or peripheral vasculopathy.

6.1.2. Organ at risk volume definition

Rectal bleeding and anorectal dysfunction are the most frequent and limiting symptoms after radiotherapy for prostate cancer. Rectal toxicity is correlated with the volume of rectum irradiated [149–151]. However, the reported rates of rectal bleeding in relation to the volume of rectum irradiated differ markedly, due probably to the lack of uniformity in the definition of the rectum between studies. Thus, in a study by Foppiano et al., the rectum was contoured from one CT slice above the anal verge up to one CT slice below the sigmoid colon [152], while in a randomized trial comparing conventional and 3-D CRT, Koper and colleagues contoured the rectum from the anal region to the level of the inferior border of the sacroiliac joints. The anal region was taken arbitrarily as the distal 3 cm [153]. Independent factors for the development of late rectal toxicity ≥ grade 1 were the rectal and anal volume exposed to ≥90% of the total dose [154]. Fiorino et al. evaluated rectum dose–volume histogram of 245 patients and found a significant reduction in rectal bleeding when the rectal volume receiving >70 Gy was <30% [155]. Miralbell et al. found that patients with small rectal volumes during planning showed a trend for enlargement of the volume during the course of radiotherapy which could result in an increase in acute and late toxicity [156]. In a recent study, De Crevoisier et al. found an increased risk of biochemical and local failure for patients whose rectum was distended during planning CT [157].

Guidelines to define the rectum are controversial as some authors recommend defining the outer wall of the rectum (i.e. the whole rectum) and others the rectal wall alone (i.e. the volume between the inner and the outer walls of the rectum) or parts of the rectum (i.e. the anterior and/or posterior rectal walls). The superior–inferior extension of the rectum contour appears to be, in addition, an important matter. As data from the literature provide no clear recommendation, a pragmatic approach would be to define the rectum 1–2 cm above and below the plane of the CTV, as doses to the rectum beyond this range would ordinarily be minimal. Others, such as the RTOG, recommend the outline of the rectum to be from the rectosigmoid down to the bottom of the ischia. Care should be taken to reduce, as much as possible, the dose to the anal canal. This critical structure might be outlined separately as an additional organ at risk, in view of the different anal toxicity to the rectum [158].

The bladder should be outlined throughout its extent with care in determining the prostate base from the bladder itself. Delineation of the external bladder contour is generally accepted with conventional and 3-D radiotherapy. With IMRT, it might be preferable to delineate an inner margin and not assume the bladder as a solid structure. The International Commission on Radiation Units and Measurements (ICRU) Report 62 recommends an additional margin for all organs at risk to take all uncertainties into account, including the variation in inter-observer organ delineation as well as organ motion [159]. The bladder volume should be maintained throughout treatment by either ensuring the emptying of the bladder before each fraction of radiotherapy or the ingestion of a repeatable quantity

of fluid prior to each treatment to ensure consistent bladder filling. Similarly, the patients should be encouraged to empty their bowels at the time of the planning CT and before each treatment.

6.1.3. Treatment planning

The planning CT may overestimate the volume of the prostate compared to transrectal ultrasound (TRUS) as reported by Hoffelt et al. [160]. They conducted a comparative study and found that CT overestimated the prostate volume by approximately 50%, compared with TRUS. Furthermore, CT may also overestimate the prostate volume compared to MRI, and the latter allows a more precise definition of the prostate apex and thus the MRI defined prostate volume may be more anatomically correct [161–163].

Recent publications recommend the use of MRI co-registered with CT for treatment planning [164–166]. However, as many use only CT for prostate cancer treatment planning, the potential overestimation of the prostate volume with CT imaging may well be appropriate, especially for patients with risk factors requiring a more generous periprostatic margin as stated above. It appears that most of the error in defining the prostate using CT occurs in four distinct regions of discrepancy: (a) the posterior portion of the prostate, (b) the posterior–inferior–apical portion of the prostate, and (c) regions corresponding to the neurovascular bundle [163]. This question becomes relevant when considering that the tissue separation at the prostate–rectum interface is much easier to define compared with the lateral or anterior parts of the prostate where the fibro-muscular tissue and the venous plexus present a similar Hounsfield unit density as the prostate gland. Thus, CT delineation of the posterior part may be more accurate than the anterior and lateral parts.

6.1.4. Patient positioning and immobilization

The debate on treatment position (either supine or prone) is still unresolved. The only randomized study comparing prone and supine patient positioning was performed by Bayley et al. [167]. They found a significant advantage in favour of a supine position with respect to prostate movement, the number of set-up corrections, patient comfort and radiation therapist convenience, as well as for all dose levels for small bowel, rectal wall and bladder wall doses. More recent studies have confirmed that there may be no benefit to using the prone position as compared to the supine position [168, 169].

There is also no agreement on which immobilization device is best or whether immobilization is necessary at all. In a randomized trial with 96 patients treated in a prone position with and without a rigid immobilization device, Kneebone et al. [170] found that port film deviations of >10 mm were reduced from 31% without immobilization to 11% with rigid immobilization [170]. Another trial comparing two immobilization devices for patients treated in a prone position was carried out by Fiorino et al., and found that leg immobilization casts were superior to pelvic abdominal immobilization casts in all directions. The latter group was also inferior to a control group of non-immobilized patients [171, 172].

In summary, it seems reasonable to state that there is more evidence in favour of supine patient positioning including the use of a knee support. Nevertheless, prone patient positioning may also be an adequate procedure provided that an efficient patient immobilization device is used.

6.1.5. Internal organ immobilization

Consistency in target organ positioning is assisted by maintaining a constant bladder volume and ensuring the emptying of the bowel before each fraction. The feasibility and reproducibility of a rectal balloon for prostate immobilization and rectum distension has been assessed by some, but challenged by others. Sanghani et al. found in a comparative planning study that the use of a rectal balloon was superior to standard radiotherapy without a balloon with respect to rectal dose–volume histograms [173]. Clinical results of patients treated with a rectal balloon also showed favourable toxicity results in a study by Teh et al. [174].

Rectal balloon positioning appears to be crucial, however. In a study by Miralbell et al., one third of patients experienced rectal probe repositioning errors [175]. Van Lin et al. carried out a study comparing 22 patients with endorectal balloon and implanted gold markers with a group of 30 patients with implanted markers only. They concluded that the rectal balloon did not help to reduce the interfraction prostate motion. Systematic prostate displacements were better managed by correcting the position based on fiducial markers [176].

6.1.6. Interstitial tissue separation

Interstitial tissue separation between the prostate gland and the ventral rectum wall can lead to a lower rectal dose in dose escalated prostate treatments [177–179] and seems to have a great potential for lowering toxicity rates. According to existing early experiences, the artificial tissue separation does not negatively influence patients' quality of life [177]. However, longer follow-up results and larger treatment cohorts are needed to confirm this initial impression.

6.1.7. Treatment verification

Treatment verification using portal imaging based on bony landmarks has been recommended. Port films or digital portal imaging techniques are compared against digitally reconstructed radiographs or simulator films at the beginning of a radiotherapy course, and periodically, once the treatment repositioning has been accepted, on a daily or weekly basis depending on treatment complexity [180]. Image guided radiation therapy (IGRT) is the latest development in treatment verification. There are different IGRT modalities available.

An ultrasound based repositioning system allows for prostate localization immediately before each radiotherapy fraction with the patient in the treatment position. According to several publications, the use of this system, first described by Lattanzi et al. [181], offers the possibility to enhance the daily prostate set-up verification and thus the accuracy of EBRT [182–185]. Langen et al., however, did not find an overall accuracy improvement of the treatment delivery after ultrasound repositioning. When compared to implanted markers, repositioning was only reliable in the antero–posterior direction but not in the supero–inferior or laterolateral ones [186]. Furthermore, in a phantom study, McGahan et al. found that moderate ultrasound probe pressure caused differences of 1 cm in the prostate localization [187].

Radio-opaque markers implanted inside the prostate can also be monitored with portal images and can help to verify the prostate position from session to session. Shirato et al. described the value of real time tumour tracking radiotherapy with implanted gold markers for various tumours [188]. The major drawback of this verification method is the potential migration of the implanted markers throughout the treatment course. Pouliot et al. did not observe significant movements of the implanted prostate gold markers and drew conclusions on their reliability as part of an accurate verification method for assessing prostate motion [189]. Others have also assessed the degree of accuracy of implanted gold markers and found a minimal motion of less than 2 mm during a course of radiotherapy [190, 191]. The major interest in improved positioning with the help of radio-opaque markers is the possibility to reduce the planning target volume (PTV) margins around the CTV. Wu et al. observed that, based on the use of gold seeds in 13 patients and the assessment of 272 port films, it was safe to reduce the PTV margins to 6 mm at the rectum–prostate interface as well as superiorly and inferiorly [192].

Cone beam CT is the third option in IGRT treatment verification. The prostate (with or without implanted markers) and surrounding soft tissues may be imaged directly before every treatment fraction and compared with the simulation CT scan. Preliminary work is now emerging but intraprostatic markers appear to improve localization even when cone beam CT is used [193–195]. A full 3-D reconstruction of the target and organs at risk is possible with this approach. An adaptive correction strategy in repeated CT scans during treatment may lead to an overall reduction in systematic error, as evaluated in a study by Hoogeman et al. [196]. Furthermore, the use of set-up correction protocols may result in a safer treatment delivery, especially when IMRT is used [197].

In summary, there are currently no universally agreed standard methods for treatment planning or verification; however, the American College of Radiology's ACR Appropriateness Criteria, which are guidelines for treatment planning, are readily available on-line. This resource provides a comprehensive set of recommendations [24]. The minimum verification method required is still portal imaging and corrections based on bony landmarks. IGRT methods allowing for set-up corrections according to the target position itself have a promising future. Since these methods of treatment verification require a potentially complex set-up correction on a daily basis, they may only be used in centres able to handle the additional workload that this represents.

6.2. POST-OPERATIVE EBRT

Patients who have undergone a prostatectomy are at a higher risk for urinary complications, especially when radiotherapy is started shortly after surgery [198, 199]. It is recommended to initiate radiotherapy after recovery from reversible post-operative urinary symptoms. Apart from the possible increased risk of side-effects due to toxicity combined with surgery, the risk for complications might, on the other hand, be reduced in comparison to definitive radiotherapy because of the smaller target volumes and lower radiation doses (60–66 Gy instead of 70–78 Gy).

6.2.1. Target volume definition

Most post-operative patients undergoing salvage radiotherapy are treated empirically without imaging [89]. In order to define the appropriate target volumes (CTV and PTV) for prostate cancer patients after prostatectomy, the probable site or sites of local recurrences based on the patients presenting and pathological information need to be assessed. A local relapse can be confirmed by physical examination, TRUS guided biopsy, CT, endorectal coil MRI, PET or by biopsy [199–202]. However, none of these are considered standard approaches. Several studies have evaluated the site or sites of a biopsy proven relapse in the prostatic bed after prostatectomy. Most sites are found in the urethro-vesical anastomosis, the bladder neck and/or the retrovesical space [203, 204]. Seminal vesicles, if retained, may be the site of relapse in 22% of patients [199]. As most recurrences occur at the level of the anastomosis between the bladder neck and the urethra, surgeons can help to define this high risk region by placing a metal marker at the level of the urethro-vesical anastomosis.

The role of MRI and PET imaging for adjuvant radiotherapy after prostatectomy still needs to be defined. However, for selected patients with a detectable PSA level, an endorectal coil MRI may help to detect macroscopic residual disease. Thus, gross tumour volume can be defined and treated with a higher dose. Miralbell et al. [200] used contrast enhanced endorectal magnetic resonance images in 60 patients with suspected local relapse (or residual disease) after radical prostatectomy, in order to help define the precise site of tumour growth. Based on this, they proposed a CTV for post-operative radiotherapy with an approximately cylindrical shape (≈ 4 cm × 3 cm) centred 5 mm posterior and 3 mm inferior to the urethro-vesical anastomosis. The use of this CTV might reduce the irradiation of neighbouring normal tissue in the pelvis and thereby potentially improve treatment tolerance.

Other investigators routinely perform TRUS to assess sites of local recurrence and use gold marker seeds implanted into the anastomoses to guide treatment using on-line imaging immediately prior to each treatment [105, 203]. This allows corrections to be made for set-up errors and target motion improving the accuracy of treatment.

The following areas are at a high risk for relapse after prostatectomy and should therefore be part of the treatment target (i.e. the prostate bed):

— Centrally: the urethro-vesical anastomosis;
— Cranially: the bladder neck;
— Caudally: including the proximal penile bulb may increase the risk of impotence but may be indicated if the apical margins were positive;
— Anteriorly: the urethro-vesical anastomosis and the bladder neck;
— Posteriorly: back to the outer rectal wall and the bladder neck;
— Laterally: the neurovascular bundles and the bladder neck.

The CTV will include the above mentioned high risk areas surrounded by 5 mm in all directions (except the rectal wall) to account for microscopical extension. The bed of the seminal vesicles will have to be included in the CTV if involved in the surgical specimen (pT3b). PTV margins may include a soft tissue rim of 5–10 mm around the CTV.

6.2.2. Treatment verification

Chinnaiyan et al. reported on the use of daily transabdominal ultrasound for targeting the prostate bed [205]. They observed significant target shifts in all directions, justifying the implementation of daily ultrasound based

set-up controls before every treatment session. However, as the accuracy of such repositioning method has been questioned for patients treated for primary prostate cancer with the organ in place, the accuracy of ultrasound based repositioning may be less reliable than expected, as reported by Paskalev et al. [206].

As mentioned earlier, implanting radio-opaque markers during surgery or prior to treatment around the urethro-vesical anastomosis may improve the accuracy of treatment [105]. Other forms of image guided radiotherapy, using cone beam CT scans, may also be used for radiotherapy verification in patients after prostatectomy. In a study by Kupelian et al, the extent of variation in the position of the prostate bed with respect to the bony anatomy was evaluated by performing a megavoltage CT before each treatment fraction [207]. They concluded that significant motion (≥3 mm) of the prostate bed with respect to the bony anatomy was infrequent. Still, the small differences might have implications for treatment margins. The authors also pointed out the importance of the definition of what should be considered as the prostate bed in estimating the movement of the target volume.

In summary, there is currently no established standard for treatment verification. It is recommended that, as a strict minimum, there should be portal imaging of bony landmarks with correction protocols at least weekly. It is recommended to develop a specific quality assurance programme for this indication in each institution.

6.3. HIGH DOSE RATE BRACHYTHERAPY TECHNIQUE

Advantages of HDR brachytherapy as compared to LDR seed implants include lower radiation exposure to treating staff, the ability to fractionate the treatment and the ability to optimize the dose distribution. Furthermore, no radioactive sources remain in the body of the patient after the procedure, which eliminates patient related post-implant radiation protection issues. Since real time TRUS based treatment planning may provide better prostate imaging quality than CT and because the procedure can be performed in the operating theatre within 10–15 minutes, this method has been recommended in many existing guidelines [208]. An up to date HDR implant procedure begins by introducing a Foley catheter following adequate anesthesia and positioning of the patient in the lithotomy position [209]. The catheter may be filled with aerated gel to improve visibility on TRUS images. After checking for potential pubic arch interference, as well as for prostate projection to the perineal template grid on the screen of the TRUS machine, a 3D TRUS volume will be created. Imaging for the volume starts at the half of the Foley balloon in the bladder and finishes at the bulb of the penis. Additional methods can help define the geographic location of intraprostatic tumor load (such as MR spectroscopy image matching, or Doppler-TRUS) and may influence the planned needle geometry within the prostate. Needles are implanted from the medial to the lateral section of the gland using axial TRUS image guidance in a proper geometry. Usually the peripheral zone and detectable areas of capsule invasion will be implanted with approximately 1 cm needle separation. If necessary, additional needles will be implanted in order to cover the apical part of the prostate. If base involvement was verified, needle tips will be inserted into the bladder, since the first possible source position is about 6–8 mm behind the trocar tip of the needle. The implantation starts in ventrodorsal direction and right/left needles will be implanted after each other to avoid procedure related torsion of the gland. Then, by the use of the sagittal view each needle will be forwarded to the base of the prostate under visual control. After finishing the implantation, a 3D TRUS volume will be created and analyzed to control needle geometry within the prostate. If necessary, improvements are easy to perform. If the geometry of the implantation was accepted, 1.0 mm transverse images via video connection from TRUS unit should be captured and transferred to the planning computer. The capture starts at least 5.0 mm cranial to the needle tips and ends 5.0 mm caudal from the apex. Volumes of interest (prostate, rectum, bladder and urethra) are delineated and the individual needle positions are corrected in the virtual 3D volume.

After creating an appropriate dose distribution and its 3-D control, the needles are connected to the afterloading machine and the fraction is delivered. Once this has been completed, the needles and potential in vivo dosimetry devices are extracted. Recommended dose constraints vary in different publications and are listed in the GEC-ESTRO (Groupe Européen de Curiethérapie/European Society for Radiotherapy and Oncology) temporary brachytherapy recommendations [208].

Slessinger et al. described the CT based HDR brachytherapy technique [210]. TRUS is used to identify the prostate and to place gold marker seeds at the base and apex. With the stepper stabilizer and template in place, needle placement is performed at the largest prostate cross-section. Needles are placed to allow for peripheral coverage with approximately 1 cm needle spacing. In addition, 2–4 interior needles, depending on the prostate size, are placed midway between the urethra and the peripheral needles. Fluoroscopy and flexible cystoscopy are used

to confirm adequate needle insertion depth. Once needle implantation has been completed, a template photograph is obtained in the operating theatre. A special CT compatible board may be used to move the patient from the operating theatre table to the CT table and to the hospital bed since stable needle insertion depth requires that leg movement be minimized. CT scanning is performed once the patient has been released from the recovery room. CT images (with diluted contrast filling the bladder) are obtained to evaluate and adjust needle insertion depth to assure adequate coverage at the prostate base. Once adjustments have been completed, rectal contrast is introduced, needle obturators are withdrawn and 2.5 mm axial CT slices are acquired from the level of the mid Foley balloon to the perineum. The needles contain only air and appear as dark spots on the CT images. After the CT, the levels where the needles emerge from the template are marked to document the catheter position. The CT study is exported to the treatment planning computer. The radiation oncologist delineates the planning target, urethra and rectal dose points. Then, implant needle catheters are reconstructed and active dwell positions are selected. Maximum urethral dose is limited to 110% of the prescription dose based on the contoured volume, and anterior rectal dose points at the rectal contrast interface are not to exceed 75%. Other constraints are that the volume receiving 125% and 150% of the prescribed dose should not be greater than 50% and 25% of the target volume, respectively. The total planned treatment time is verified using an independent method. A range of doses has been deemed acceptable. Slessinger et al. recommend 950 cGy followed 7 days later by another implant delivering another 950 cGy, when the brachytherapy is being administered as a boost to supplement external beam radiation. Patients who are treated with monotherapy receive 6 HDR treatment fractions (700 cGy/fraction). For monotherapy, the patient has two operating theatre procedures, each associated with an operating theatre day treatment, and two fractions the following day, a minimum of 6 h apart. The following day, radiographic imaging is obtained. Adjustments to catheter insertion depth are made based on comparison with the baseline orthogonal film set obtained shortly after the planning CT.

It is important to note that on completion of each treatment session, the patient is surveyed with a calibrated radiation instrument to confirm that the HDR source has been safely stored.

7. THE ROLE OF ANDROGEN DEPRIVATION IN NON-METASTATIC PROSTATE CANCER

ADT has a role in radical (curative) and palliative treatments. The use of ADT in radical treatment (neoadjuvant and adjuvant therapy with radiotherapy) has been discussed in earlier sections.

The effect of ADT on prostate cancer has been well described since the original reports of Huggins and Hodges [211, 212]. For patients who are unsuitable for radical treatment (e.g. those with metastatic disease) or who have failed radical treatment, ADT remains the mainstay of therapy. Surgical castration (bilateral orchiectomy) has been the gold standard for such patients until the development of the medical alternative via the use of LHRH-a in the 1970s [213]. The availability of sustained release formulations allowed an alternative to bilateral orchiectomy in patients with late stage disease or metastases [214].

7.1. MAXIMUM ADT

Bilateral and medical orchiectomy removes 90–95% of circulating serum testosterone (the amount that is produced by the testes). The remainder is largely derived from synthesis in the adrenal glands. As such, to achieve maximum androgen deprivation, an antiandrogen can be given in combination with an orchiectomy.

There is a small advantage in overall survival with maximum ADT with added anti-androgen. However, the toxicity of this combination may outweigh any potential gains [215]. There are also considerations of cost and compliance. Patients already orchidectomized who progress should be considered for maximum ADT [215–217].

7.2. ANTI-ANDROGEN DRUGS

Both steroidal and non-steroidal anti-androgens have been used in the systemic therapy of prostate cancer. The steroidal anti-androgen cyproterone acetate is not recommended as a monotherapy because of its lack of efficacy compared to LHRH antagonists in delaying the progression of metastatic disease [218]. In addition, the normal therapeutic dose of cyproterone acetate (200–300 mg daily) required to achieve androgen blockade is associated with hepatotoxicity, thromboembolic phenomena, weight gain, shortness of breath and peripheral oedema (fluid retention). However, in smaller doses (50–100 mg), cyproterone may have a role in the amelioration of the hot flushes associated with ADT [219].

Non-steroidal anti-androgens may be used as a monotherapy in men who wish to preserve some degree of sexual interest and performance, but at the risk of associated side-effects, particularly gynaecomastia and mastalgia, and possible hepatotoxicity. Flutamide has been reported to cause additional gastrointestinal upset (diarrhoea), while bicalutamide and nilutamide have been more favoured as they are less likely to cause this particular problem [220].

Whichever form of anti-androgen is used, daily dosage is required. This may result in compliance issues as well as availability and cost related issues in certain parts of the world.

7.3. SIDE-EFFECTS

The side-effects of ADT are well described and are related to the loss of testosterone [219, 221]. These include: weight gain (increase in body fat); sarcopaenia (loss of muscle mass and tone); joint aches; osteopenia/osteoporosis (leading to an increased risk of fractures); mood/psychological changes; cognitive impairment; hot flushes; metabolic syndrome; dyslipidaemia (↑LDL and TriG, ↓HDL); insulin resistance (or worsening of pre-existing diabetes); cardiac effects; anaemia; elevated blood pressure; loss of libido and impotence; gynaecomastia and mastalgia; genital atrophy; skin dryness; loss of body hair (reversal of male pattern baldness); and idiosyncratic drug reactions.

These side-effects can impact significantly on the quality of life of patients, particularly if ADT is given for a prolonged or continuous period, but such side-effects may even be present when ADT is delivered intermittently [222]. The impact may be ameliorated with an intermittent approach to the delivery of the ADT, but only if medical castration has been performed (not surgical orchiectomy) to allow for some recovery of serum testosterone levels. In addition, if an anti-androgen is used to achieve maximum androgen blockade, there are additional potential toxicities from these drugs.

While side-effects are generally reversible with short term use of ADT in the form of LHRH agonists, there are concerns about longer term toxicities and speculation on potential morbidity in older patients [223]. The recommendation is that all practitioners should be aware of the potential side-effects and should be proactive in the management of these effects [223].

7.4. COSTS

As mentioned in the preceding sections, ADT can have a significant negative impact on patients' quality of life. In addition, there are medical resource and economic considerations in the use of ADT. The administration of LHRH-a and anti-androgens requires supervision of the patient by medical and nursing staff who are trained and experienced in the use of these medications, as well as in the management of potential side-effects. In many developed countries, the health infrastructure to support intensive follow-up of such patients exists. This may not be the case in countries where health care resources are limited.

The economic costs of ADT should be considered pragmatically. The costs of LHRH-a compared to surgical bilateral orchiectomy is shown in Table 4 [224], taking Australia as an example. There are costs to the individual patient and the healthcare system. If similar comparative costs exist in other countries around the world, the economic benefit of bilateral orchiectomy, combined with the potential inconvenience of compliance issues, may mean bilateral orchiectomy is the most cost effective means of ADT in the management of prostate cancer in the context of health care systems with limited resources for other treatments.

TABLE 4. DATA FROM PHARMACEUTICAL BENEFITS SCHEME AND MEDICARE BENEFITS SCHEDULE, AUSTRALIA [224]

Medication	$[a]
Goserelin 3.6 mg (1 month duration of action)	213.76
Leuprorelin 7.5 mg (1 month duration of action)	269.39
Goserelin 10.8 mg or leuprorelin 22.5 mg (3 months' duration of action)	711.27
Bilateral orchiectomy (general surgeon)	177.54
Bilateral orchiectomy (urologist)	241.59

[a] Converted from Australian dollars using the exchange rate in February 2009: 1 AUD = 0.643 US$.

7.5. RECOMMENDATIONS

Many countries and organizations have developed and published guidelines for the treatment of prostate cancer accompanied by critical appraisals of the published literature [208, 216, 217, 225–231]. Where resources are limited, the adoption of a pragmatic but balanced treatment policy cognizant of the healthcare and socioeconomic needs of patients is important.

The survival of men who require ADT varies depending on the extent of the disease. In men without overt metastases who are receiving ADT, overall survival may be 10 years or more [215]. On the hand, in patients with metastases, the median overall survival ranges between 28 and 53 months [232]. Patients who progress while receiving ADT (castrate resistant prostate cancer) should be considered for second line ADT, bisphosphonate therapy and chemotherapy.

8. FOLLOW-UP

As a follow-up, a PSA is recommended at 3 months post-treatment, and every 6 months thereafter, with an annual digital rectal exam. The American Brachytherapy Society follow-up guidelines for prostate patients following HDR brachytherapy include serial PSA measurements, baseline at 3–6 months and then every 3–6 months, as well as an annual digital rectal examination [233]. They also recommend quality of life assessment and that urinary, bowel and sexual functions should be prospectively assessed at follow-up visits.

NCCN guidelines do not distinguish between types of treatment with regard to follow-up recommendations. They recommend a PSA every 6–12 months for the first 5 years and then annually thereafter. This is a reasonable approach when we consider the time after which post-treatment recurrence occurs. For example, 45% of recurrences occur within the first 2 years, 77% by 5 years and 96% by 10 years [87].

9. RECOMMENDED STRATEGIES

The following figs 1–4 summaries the recommended strategies for the management of localized prostate cancer in a diagrammatic format.

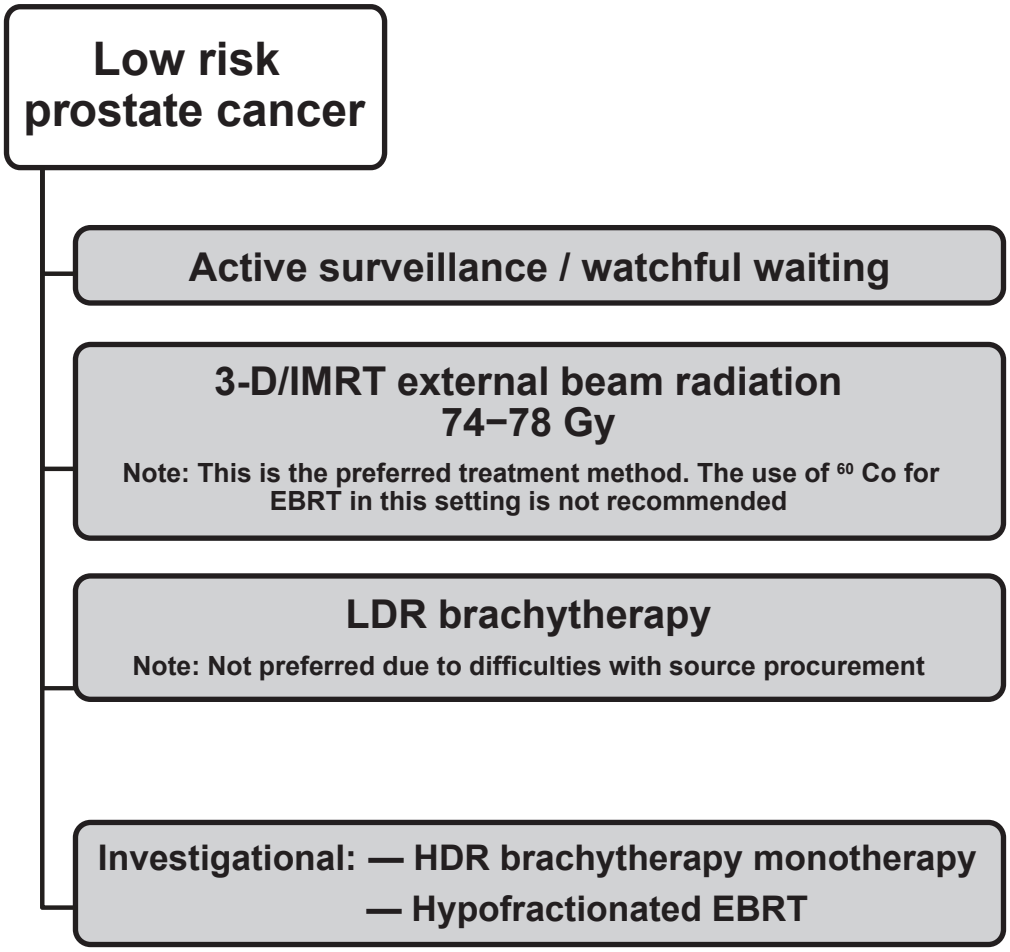

FIG. 1. Strategies for the management of low risk prostate cancer.

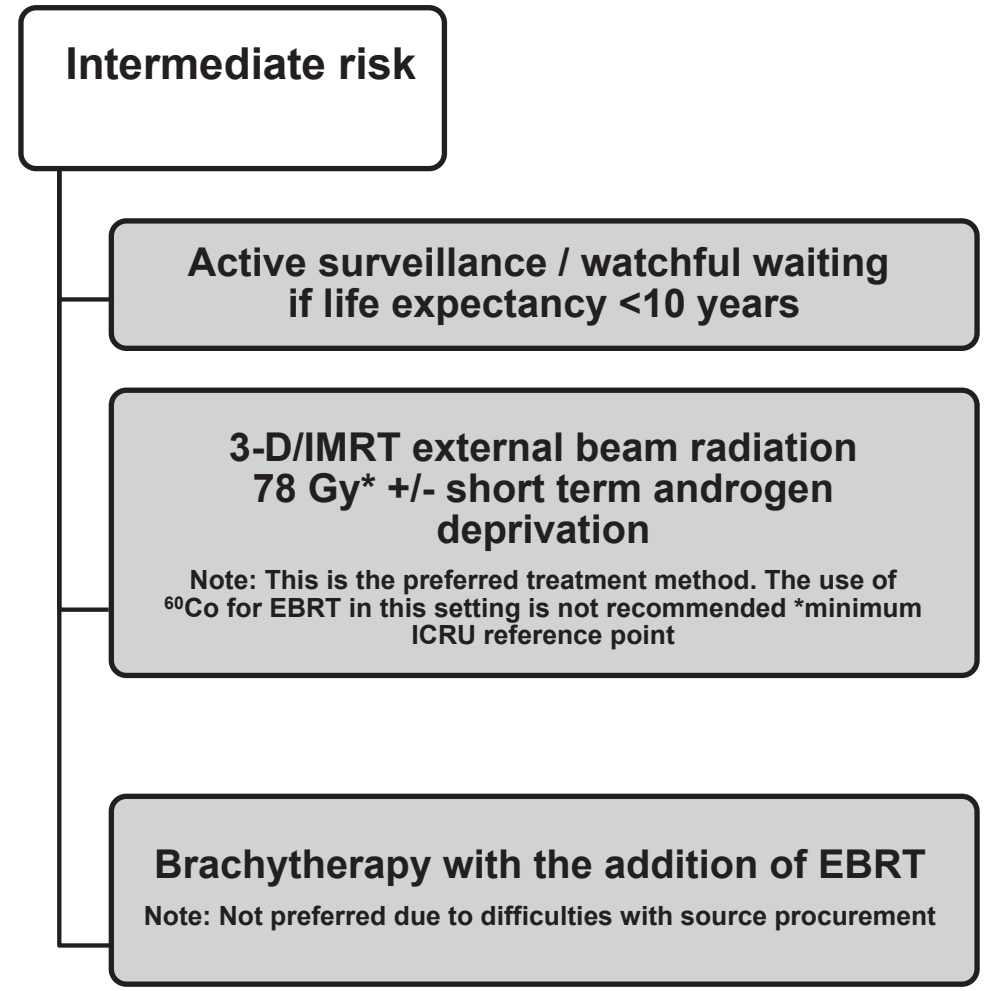

FIG. 2. Strategies for the management of intermediate risk prostate cancer.

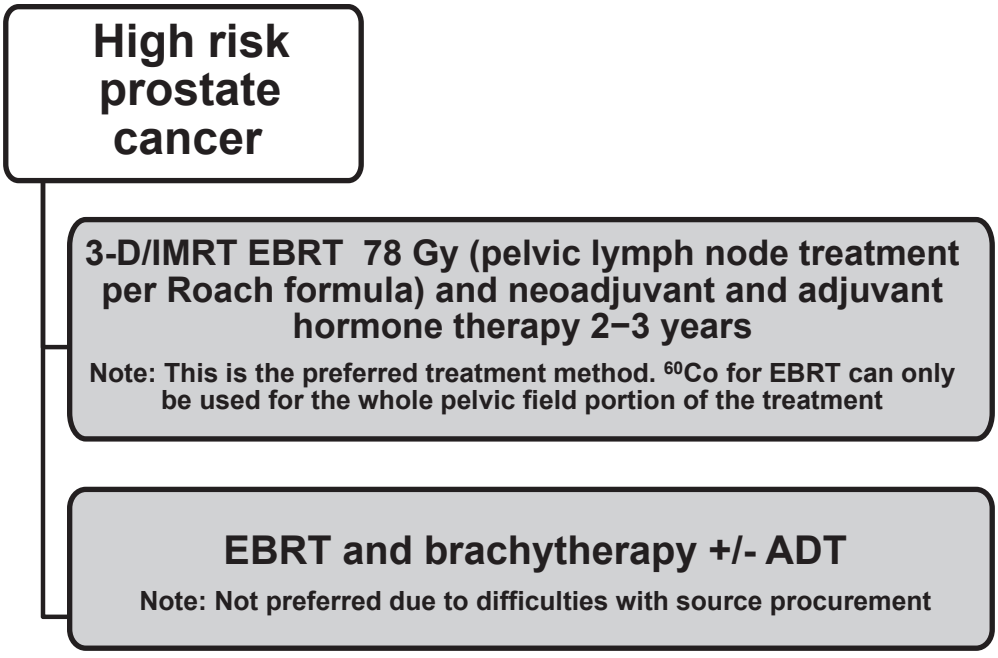

FIG. 3. Strategies for the management of high risk prostate cancer.

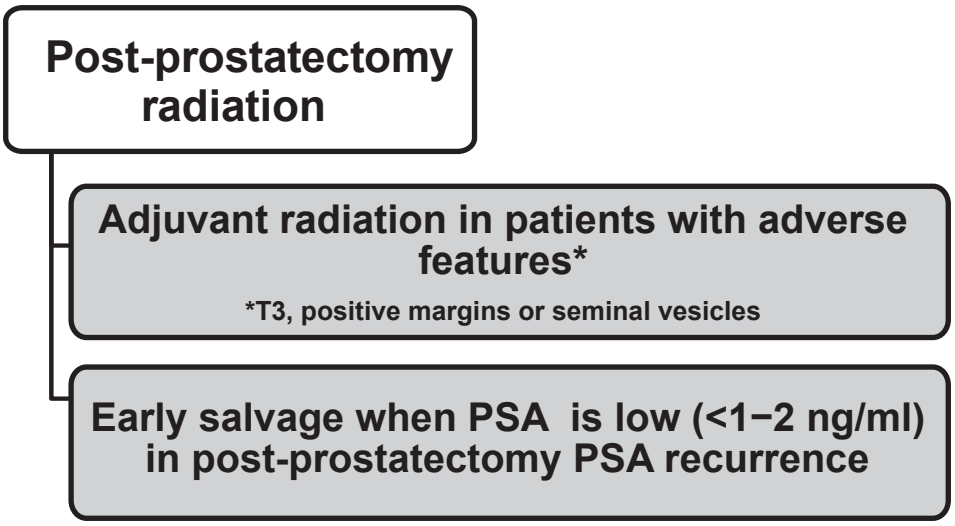

FIG. 4. Strategies post-prostatectomy radiation.

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