

# Radical Radiotherapy for Prostate Cancer

Mererid Evans and Malcolm D. Mason

## Key Points

1. There have been no randomised trials comparing brachytherapy or IMRT with conventional radiotherapy.
2. ADJUVANT radiotherapy has recently been shown to improve progression-free survival after radical surgery in patients with tumour at excision margins or infiltrating seminal vesicles.
3. Hormone therapy improves outcomes (progression free survival and survival) after radical radiotherapy for locally advanced disease.

## Introduction

The incidence of prostate cancer is rising worldwide due to the ageing of the population and the increasing availability of prostate-specific antigen (PSA) screening. Prostate-specific antigen testing has led specifically to an increase in the proportion of patients diagnosed with early-stage (localized) prostate cancer. Radical radiotherapy is one of the curative treatment options for localized prostate cancer and it also has a role to play in locally advanced and even metastatic disease. This chapter reviews the relative merits of radiotherapy in comparison to the

other management options for early prostate cancer and summarizes the staggering technological advances that have occurred in prostate radiotherapy over the last decade.

## **Treatment of Early (Localized) Prostate Cancer**

### **The Role of Radical Radiotherapy**

The optimum management of patients with localized prostate cancer remains controversial. Three major treatment options are available: radical prostatectomy, radical radiotherapy (external beam radiotherapy [EBRT] or brachytherapy), and active surveillance (also known as active monitoring and watchful waiting). Each treatment involves its own risk. Radical treatments can cause harmful side effects including incontinence, erectile dysfunction, and even death, whereas watchful waiting causes anxiety relating to the presence of cancer and carries a risk of disease progression. However, outcomes in terms of overall survival appear similar with each of the three modalities.

There is relatively little randomized evidence concerning the effectiveness of the different management options for early prostate cancer. In a Scandinavian study [1], men with early prostate cancer (stages T1b-c or T2) were randomly assigned to radical prostatectomy or watchful waiting. After a median follow-up of 6.2 years, there was a significant reduction in disease-specific mortality in the radical prostatectomy group compared with the watchful waiting group (4.6% vs. 8.9%,  $P = .02$ ), but there was no significant difference in overall survival between the two groups. A randomized trial comparing surgery with radiotherapy published in 1982 showed better survival outcomes in the surgery group [2]. However, this was a small (97 patients), single-center trial conducted in the pre-PSA era, and it is unlikely to be relevant to contemporary practice. Unfortunately, a United Kingdom Medical Research Council (MRC) trial (PR06) randomizing patients to radical prostatectomy, radical radiotherapy, and watchful waiting was closed in 1997 because of poor recruitment, which was attributed to an unwillingness among participants and clinicians to accept randomization.

A number of nonrandomized, retrospective studies have compared the outcomes of the different treatment modalities for early prostate cancer. A study from Boston compared outcomes in 2254 men treated with radical prostatectomy and 381 men treated with conventional dose (66 Gy) radiotherapy [3]. There was a possible advantage for surgery in low-risk patients, but no difference between treatment modalities in intermediate or high-risk cases. Another study from the Cleveland Clinic compared outcomes in 1054 men who underwent radical prostatectomy and 628 treated with radiotherapy [4]. When stratified by prognostic risk groups, there was no difference in biochemical control between patients undergoing prostatectomy and patients having radiotherapy to dose levels  $\geq 72$  Gy; however, the outcome of patients who received lower-dose radiotherapy was less favorable. There are many problems with retrospective comparisons like these, including differences in case selection and length of follow-up, and the inherent disadvantages of analyzing past rather than contemporary practice.

At least two large randomized trials are currently in progress, although their results are not yet available. The United States Prostate Cancer Intervention Versus Observation Trial (PIVOT) is comparing radical prostatectomy and watchful waiting for localized prostate cancer [5]; it opened in 1994 and has now closed to recruitment. The U.K. Protect study (*Prostate Testing for Cancer and Treatment*) combines the identification of men with prostate cancer detected by PSA screening with a randomized trial comparing radical prostatectomy, radical EBRT, and watchful waiting. The issue of randomization to the various treatment options was successfully addressed in a feasibility study, which has aided recruitment into this study, and has shown that with careful management, it is possible to randomize prostate cancer patients into trials such as this.

While the results of these studies are awaited, clinical decision making in early prostate cancer should be tailored to the individual patient and take account of tumor prognosis (Gleason grade, stage, and PSA), background health, life expectancy, and patient preference. It is common to offer curative treatment to men who have a life expectancy of 10 years or more and to consider treatment for men with a life expectancy of 5 years or more if the tumor is poorly differentiated. Treatment-related morbidity and quality-of-life issues are important considerations and patients should be counseled appropriately. Prostatectomy

patients are significantly more likely than radiotherapy patients to experience urinary incontinence (39% to 49% vs. 6% to 7%) and erectile dysfunction (80% to 91% vs. 41% to 55%), whereas radiotherapy patients are more likely to experience bowel urgency (30% to 35% vs. 6% to 7%) [6].

## **Standard External Beam Radiotherapy (EBRT)**

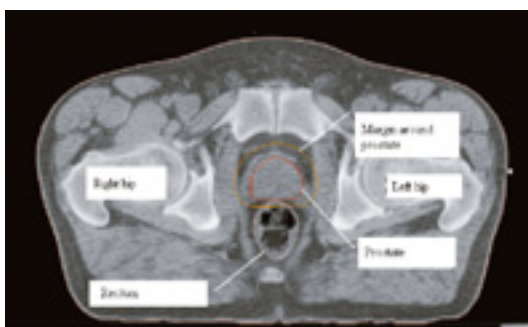
Radical EBRT is an alternative to radical prostatectomy for patients with early, organ-confined prostate cancer (T1-2, N0, M0) and can also be used for patients with nonmetastatic locally advanced disease (T3-T4) where surgery is inappropriate.

### **Pretreatment Assessment**

The primary tumor is assessed by digital rectal examination, cystoscopy, and transrectal ultrasound (TRUS). Staging of systemic disease usually comprises bone scanning and pelvic lymph node imaging (with computed tomography [CT] or magnetic resonance imaging [MRI]), although these investigations are sometimes omitted in patients with particularly “good risk” features. Magnetic resonance imaging scanning is particularly useful in assessing capsular invasion, seminal vesicle involvement, and periapical extension, and can aid treatment planning.

### **Treatment Planning**

Computed tomography planning is now standard practice in most U.K. centers. Prior to the advent of CT planning, the size and position of the prostate was indirectly visualized using a cystourethrogram, putting barium in the rectum and taking orthogonal films, upon which the target volume could be drawn. The target volume is usually defined as the prostate plus all/base of the seminal vesicles, or any grossly visible tumor, with a margin of 1 to 1.5 cm to allow for microscopic spread and for variations in treatment setup (Fig. 1.1). A smaller margin is often allowed at the rectal-prostate interface if there is too much rectum in the high-dose volume. In the absence of macroscopic disease in the seminal vesicles, there is some debate as to whether they should be included in the treatment volume or not. Simple formulas for predicting the probability of microscopic seminal vesicle involvement based on the T stage, Gleason score, and pretreatment PSA level can be helpful.



**Fig. 1.1.** Computed tomography (CT) scan through the center of the target volume showing the rectum, femoral heads, prostate (or clinical target volume, CTV), and a margin around the prostate to be treated to high dose (the planning target volume, PTV).

Inconsistencies in treatment volume definition occur among clinicians [7], especially in outlining the prostatic apex, superior aspect of the prostate projecting into the bladder, seminal vesicles, the base of the seminal vesicles, and superior rectum. These should be considered when designing and comparing trials of radiotherapy.

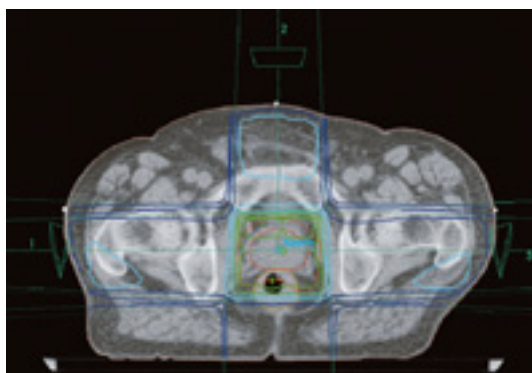
## Technique

Patients are treated in the supine position with a full bladder (this helps push bowel out of the high-dose area), once daily, 5 days a week. Skin tattoos are placed anteriorly over the pubic symphysis and laterally over the iliac crests to aid treatment setup. Three-field techniques using an anterior and two posterior oblique fields are commonly used, although four- and even six-field techniques are used in some centers (Fig. 1.2).

## Dose and Fractionation

The optimum dose and fractionation schedule for EBRT is unclear. Until recently, standard treatment schedules in many centers delivered daily fractions of 1.8 to 2 Gy per day, to a total dose upwards of 64 Gy.

There is evidence that the  $\alpha/\beta$  ratio for prostate cancer may be as low as 1.5, comparable to late-responding normal tissues,



**Fig. 1.2.** Three-field technique for prostate radiotherapy showing the 10, 20, 50, 70, 90, 95, 100, and 102 isodoses. The CTV, PTV, and rectum are outlined.

probably because of the slow turnover rate of prostate tumors [8]. This suggests that prostate cancers may be particularly sensitive to hypofractionation and that using larger fraction sizes could result in greater cell kill. In addition to the possible radiobiological gains, other benefits to hypofractionation include shorter overall treatment times and a smaller number of hospital visits, which increases patient convenience and reduces resource utilization.

The outcome of 705 men with T1-4 prostate cancer treated in Manchester with conformal, hypofractionated radiotherapy (50 Gy in 16 daily fractions) has been analyzed [9]. The 5-year biochemical-free survival rates for good, intermediate, and poor prognostic groups were 82%, 56%, and 39%, respectively, which are comparable to published results using conventional fractionation, and normal tissue toxicity rates were not increased. The results of the first randomized study of hypofractionated radiotherapy for localized prostate cancer were presented at the 45th annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) [10]; 936 patients with T1/T2 prostate cancer were randomized at 16 Canadian centers to receive either 66 Gy in 33 fractions over 6½ weeks or 52.5 Gy in 20 fractions over 4 weeks. After a median follow-up of 59 months, the treatment failure rate appeared to be slightly higher in the

hypofractionated arm than in the conventional arm, but there was no significant difference between the two groups in biopsy positivity 2 years after radiotherapy or in overall survival (with a trend for both in favor of the hypofractionated arm). Also, although acute toxicity was higher in the hypofractionated group, late toxicity was similar in both groups.

The development of conformal radiotherapy has led to a surge of interest in dose escalation (above 70 Gy), which is discussed later in the chapter.

## Toxicity

The side effects of EBRT can be divided into acute and late reactions. Acute reactions start about halfway through a course of treatment and principally involve the bladder (cystitis) and bowel (proctitis, occasional enteritis). These effects normally settle with conservative management within 4 to 6 weeks of the end of treatment. Rarely, severe acute side effects may necessitate a break in treatment, but it is unusual for acute effects to be dose limiting in practice. It is rare for patients to experience significant skin toxicity with EBRT, though a reaction is not infrequently seen superior to the natal cleft due to the exit dose from the anterior beam in a three-field arrangement.

Late side effects are generally more “dose-limiting” than acute effects because they can have a significant impact on quality of life and are often permanent. They may appear between 6 months and 2 years after radiotherapy, although sometimes acute effects do not settle and can continue as late effects. Late urogenital toxicity manifests as chronic cystitis, urinary incontinence (2% to 11%) and erectile dysfunction (10% to 40%). Late damage to the rectum results in late radiation proctitis, rectal ulceration, or stricture; severe damage occasionally necessitates a defunctioning colostomy (risk <1%).

## Efficacy

The outcome of patients treated with modern, high-dose radiotherapy is comparable to surgery, at least over a 5-year period. Five-year actuarial biochemical relapse-free survival rates of 90% have been reported for favorable risk patients treated with >75 Gy [11]. Pretreatment PSA level, Gleason score, tumor stage, radiation dose (<70 Gy or ≥70 Gy), and treatment year are all significant prognostic factors. The posttreatment PSA nadir has

been found to be highly predictive of outcome; in one study, 75% of patients with a PSA nadir of  $<0.5$  ng/mL had PSA disease-free survival (DFS) at 8 years compared to only 12% of patients with a PSA nadir  $>4$  ng/mL [12].


## Three-Dimensional Conformal Radiotherapy (3D-CRT)

Conventional radiotherapy is delivered using rectangular-shaped treatment fields, which inevitably encompass large volumes of normal tissues as well as the required target volume. The major focus over the last decade has been the development of conformal radiotherapy techniques, which allow delivery of irregularly shaped fields that conform more closely to the tumor target while reducing the radiation to the dose-limiting normal tissues. Shaping of fields can be achieved in one of two ways: by putting a custom-made lead shield in front of the beam, or by making the beam itself irregular in shape by using multileaf collimators (MLCs) (Fig. 1.3).

### Does Conformal Radiotherapy Reduce Toxicity?

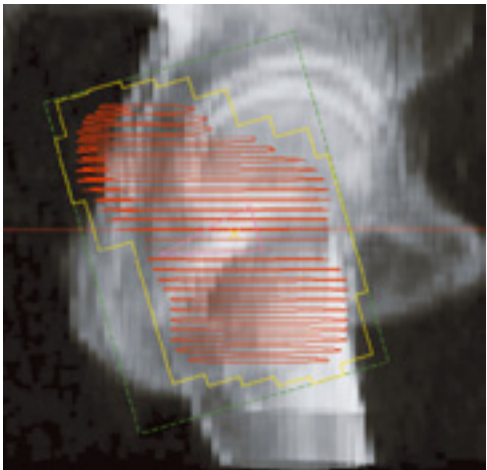
A randomized study comparing conventional and conformal radiotherapy at a standard dose of 64 Gy [13] showed a significant reduction in late ( $>3$  months after treatment) radiation-induced proctitis and bleeding in the conformal group compared with the conventional group (5% vs. 15%, Radiation Therapy Oncology Group [RTOG] grade 2 or higher,  $p = .01$ ). There were no differences between groups in bladder function after treatment. After a median follow-up of 3.6 years, there was no significant difference between groups in local tumor control: conformal 78% (95% confidence interval [CI] 66–86); conventional 83% (95% CI 69–90). These results have provided the basis for dose-escalation studies in an attempt to improve local tumor control with acceptable toxicity.

---



**Fig. 1.3.** (a) Beam's-eye view of right lateral treatment field for conformal prostate radiotherapy. Field shaping has been achieved by the use of multileaf collimators (MLCs) (shown in yellow). The collimator angle has been optimized to conform to the posterior edge of the PTV (shown in red) to protect the rectum. (b) The multileaf collimator.





A



B

## Dose Escalation

In a randomized dose-escalation trial conducted at the M.D. Anderson Cancer Center, 305 men with localized (T1 to T3) prostate cancer were randomized to receive either conventional-dose (70 Gy) or high-dose (78 Gy) conformal radiotherapy to the prostate and seminal vesicles [14]. With a median follow-up of 60 months, the biochemical control rates at 6 years were significantly higher in the 78-Gy arm compared to the 70-Gy arm (70% vs. 64%,  $p = .03$ ). Subgroup analysis suggested that the benefit of dose escalation was limited to patients with a pretreatment PSA of  $\geq 10$  ng/mL (biochemical control rate, 62% vs. 43%,  $p = .01$ ) but that there was no significant dose response in patients who had a pretreatment PSA of  $\leq 10$  ng/mL. The trial did not show a significant effect of dose escalation on overall survival, although there was a trend toward a higher freedom from distant metastasis rate at 6 years in patients with PSA levels  $> 10$  ng/mL who were treated with 78 Gy (98% vs. 88%,  $p = .056$ ). Rectal side effects were significantly greater in the 78-Gy group (grade 2 rectal toxicity rates at 6 years, 26% vs. 12%,  $p = .001$ ), whereas the rate of bladder complications was similar in both arms. The risk of rectal toxicity correlated highly with the proportion of the rectum treated to  $> 70$  Gy, and it was suggested by the authors that the rectal volume receiving  $\geq 70$  Gy should be limited to  $< 25\%$  in future dose escalation trials. The ongoing RTOG 94-06 trial is attempting to establish the maximum tolerated dose that can be delivered to the prostate using 3D-CRT. Interim results for patients treated to 79.2 Gy using 1.8-Gy fractions have demonstrated low levels of toxicity [15], and the study has continued using 2-Gy fractions to dose levels of 74 and 78 Gy.

The M.D. Anderson data are supported by data from a number of retrospective and prospective PSA-era trials that have provided evidence for a dose response in prostate cancer. However, more studies are required to define the groups of patients who may benefit from dose escalation and to assess whether there is any benefit in terms of survival. It is possible that conventional doses are sufficient in low-risk patients and that dose escalation may just increase toxicity with no benefit in terms of disease control in these patients. The results of several randomized trials of dose escalation in the UK, the Netherlands, France, and North America are awaited. The UK MRC RT01 trial, which randomized men to standard-dose (64 Gy) or high-dose (74 Gy) con-

formal radiotherapy in addition to neoadjuvant androgen suppression, closed to accrual in 2001 with around 800 patients randomized.

## **Intensity-Modulated Radiotherapy**

Intensity-modulated radiotherapy (IMRT) is an advanced form of 3D-CRT that allows tighter conformation to the target volume and sparing of normal tissues in the vicinity of and even within the target volume to an extent that was not previously possible. In general, IMRT uses inverse treatment planning systems that work backward from a desired dose distribution to generate treatment fields with varying intensities across the cross section of the beam. Treatment delivery utilizes MLCs where each set of opposing leaves travel across the beam under computer control during radiation delivery according to a prescribed scheme, to produce the required intensity pattern across the beam.

Early toxicity and biochemical outcomes have been reported for 772 patients with localized prostate cancer treated with high-dose IMRT (81 to 86.4 Gy, 1.8 Gy/fraction) at the Memorial Sloan-Kettering Cancer Center [16]. Intensity-modulated radiotherapy was associated with decreased rectal toxicity, and the actuarial rate of grade  $\geq 2$  proctitis at 3 years was only 4% compared to the rate of 14% previously reported at the same center for patients receiving 81 Gy with 3D-CRT [11]. The 3-year actuarial PSA relapse-free survival rates were comparable to published results using 3D-CRT; however, median follow-up was only 24 months and longer follow-up is required to substantiate these results. Preliminary results using hypofractionated IMRT (70 Gy at 2.5 Gy/fraction) show similar rates of late toxicity and biochemical outcome to high-dose 3D-CRT [17], although again, longer follow-up is required.

Although prophylactic pelvic lymph node radiotherapy is not routine practice in the U.K., there is evidence from the RTOG 9413 study that it may be beneficial in carefully selected patients [18]. The potential of IMRT to irradiate pelvic lymph nodes while sparing critical pelvic organs has been investigated [19]. Conventional radiotherapy plans were compared to 3D-CRT and IMRT plans for 10 patients. The mean percentage volume of small bowel receiving  $>45$  Gy for the conventional radiotherapy, 3D-CRT, and IMRT plans were 21%, 18%, and 5%, respectively,

( $p < .001$ ). The rectal and bladder volumes irradiated with doses  $\geq 45$  Gy were also reduced by IMRT. The reduction in critical pelvic organ irradiation seen with IMRT may reduce side effects and allow modest dose escalation. A phase I dose-escalation trial has been initiated to assess the tolerance of radiotherapy to the pelvic lymph nodes of 50 to 60 Gy using IMRT.

Concerns have been raised that reducing treatment volumes to such an extent carries a risk of incurring a geographical miss of the target, which would inevitably result in reduced tumour control. However, results so far suggest that PSA outcomes after IMRT are comparable to conventional 3D-CRT, although mature data are not yet available. Other potential drawbacks to IMRT include the added workload on physicians, physicists, and radiotherapists, the risk of errors due to the complexity of planning and delivery, and the complexity of quality assurance. An additional concern is that IMRT may lead to an increase in the incidence of second malignancies. There are two reasons for this: (1) IMRT involves the use of more fields than conventional radiotherapy and, as a consequence, a larger volume of normal tissues is exposed to low radiation doses; (2) IMRT usually requires more time to deliver a specified dose than conventional radiotherapy (hence more monitor units needed) thus increasing the total body exposure, due to leakage radiation. Careful long-term follow-up of patients treated with IMRT is necessary to address this issue.

## Prostate Brachytherapy

Prostate brachytherapy involves placement of radioactive sources directly into the parenchyma of the prostate. It is a highly conformal form of therapy, permitting dose escalation to the target volume far exceeding that of other radiation modalities. The surrounding normal tissues are spared because of the rapid dose falloff with distance from the source (inverse square law). The evolution of TRUS imaging, a closed transperineal approach, and the increasing sophistication of computerized planning have resulted in a worldwide resurgence of interest in this treatment technique. Its appeal lies in its speed and convenience (it can be done as an outpatient procedure) and the low long-term risk of proctitis; impotence is also less likely than after radical prostatectomy. Brachytherapy to the prostate can be deliv-

ered either with permanent seed implants or with removable implants, which are often delivered at a high dose rate with iridium wire.

## Permanent Implants

Permanent implants may be used alone as monotherapy for localized prostate cancer or, less commonly, as a boost in combination with EBRT. Patient selection is extremely important for two reasons: (1) to identify patients who are likely to have a good outcome in terms of biochemical disease free survival, and (2) to identify patients who will have a good functional outcome. Patients who are likely to have a good outcome from brachytherapy alone have an initial PSA level  $<10$  ng/mL, Gleason score  $\leq 6$ , and low-volume disease with a low risk of extracapsular spread (stage T1/T2). If the prostate is large ( $>50$  cm<sup>3</sup>), the pubic rami may shield part of the gland that cannot be adequately implanted; these patients also need a large number of seeds and are at increased risk of morbidity. If otherwise suitable, neoadjuvant hormone treatment with a luteinizing hormone-releasing hormone (LHRH) analogue for 3 months can lead to a reduction in prostate volume of  $>30\%$ . Brachytherapy should be avoided in men with a history of transurethral resection of the prostate (TURP) because it increases the risk of long-term urinary incontinence following brachytherapy from 1% to  $\sim 12.5\%$ . An alternative procedure may also be preferable in patients with significant pretreatment lower urinary tract obstructive symptoms who are more likely to develop urinary retention after brachytherapy.

Two isotopes are used as the radioactive seed source, iodine ( $^{125}\text{I}$ ) and palladium ( $^{103}\text{Pd}$ ), although only  $^{125}\text{I}$  is readily obtainable in the U.K. Both isotopes have low energy but different half-lives (59.4 days for  $^{125}\text{I}$ , 16.97 days for  $^{103}\text{Pd}$ ) and initial dose rate.  $^{103}\text{Pd}$  has the higher dose rate and is biologically more active; therefore, equivalent prescribed doses are lower. For patients treated by brachytherapy alone, typical doses are 145 Gy with  $^{125}\text{I}$  and 100 Gy with  $^{103}\text{Pd}$ , which is the minimum peripheral dose to the margin of the target volume. If brachytherapy is used in conjunction with EBRT, typically prescribed doses are 45 Gy in 25 fractions given by EBRT followed by 110 Gy via an  $^{125}\text{I}$ -brachytherapy implant [20].

A two-stage technique is most commonly used for permanent implantation in the U.K. The initial stage requires a preplanning TRUS examination performed with the patient in the lithotomy position, done either as an outpatient or day-hospital procedure under general anesthesia. The TRUS images are digitized to produce a 3D model of the prostate on the planning computer, which can be used to determine the number and position of seeds required. The implant is performed a few weeks later in an identical lithotomy position. Thin needles are inserted percutaneously into the prostate through a perineal template to a precalculated depth guided by an ultrasound probe in the rectum. The needles may either be preloaded with the appropriate number of seeds or the seeds can be inserted individually. Between 20 and 30 needles containing 60 to 120 seeds are implanted depending on the volume and seed activity. The needles are then removed, leaving the seeds permanently in place. A CT scan is performed after implantation to identify the seeds and prostatic outline, and this information is used to calculate the actual dose delivered to the prostate.

Almost all patients develop urethritis of variable intensity which may last for ~3 months. Symptoms may be helped by alpha-blockers and nonsteroidal antiinflammatory drugs. A minority of patients (15%) develop acute retention either immediately or in the few days following implantation. This is usually due to postimplant edema and requires catheterization. In most patients, micturition resumes within 2 weeks as edema resolves, although recovery may occasionally take longer. Long-term effects include persistent cystitis and prostatitis (3%), proctitis (2%), and impotence (25%). The risk of urinary incontinence is small (~1%) unless patients have had a previous TURP.

There have been no randomized trials comparing brachytherapy with other interventions for early prostate cancer (though a trial randomizing patients to brachytherapy or radical prostatectomy is now open, under the auspices of the American College of Surgeons). Most results come from single centers reporting retrospective series [e.g., 21]. These results are extremely promising, but what is difficult to gauge is the extent to which such results reflect the benefit of brachytherapy per se, and to what extent they reflect patient selection factors. Some workers advocate EBRT in conjunction with brachytherapy for patients with intermediate and high risk factors, but it is not yet proven whether this improves outcome.

## High Dose Rate Brachytherapy

Remote afterloading systems can also be used with TRUS and template guidance to deliver temporary, high dose rate (HDR) brachytherapy to the prostate. The isotope used is iridium ( $^{192}\text{Ir}$ ), which has higher emission energies than  $^{125}\text{I}$  and  $^{103}\text{Pd}$ . The greater range may be more suitable for the treatment of patients with bulkier tumors and the possibility of extracapsular extension. Treatment is hypofractionated (with the potential benefits of hypofractionation previously discussed) and treatment times are a few minutes only. Most trials investigating the usefulness of HDR to date have given it as a boost (8 to 10 Gy  $\times$  2) prior to, during, or after EBRT (45 to 50 Gy) with good results even in patients with unfavorable prostate cancer [22]. More recently, a number of HDR monotherapy trials [e.g., 23] have shown that the treatment is feasible and well tolerated, but longer follow-up is required for outcome.

## Combined Radiotherapy and Hormone Therapy

The use of combined modality treatment, with hormone therapy and radiotherapy, for the treatment of prostate cancer may be beneficial for two reasons. First, by combining two effective modalities, there is hope that the anticancer effects will be additive. Second, the use of hormone therapy to shrink a large prostate before irradiation may improve efficacy by reducing the tumor burden and also may reduce rectal toxicity by reducing the volume irradiated to high dose [24]. The LHRH agonists (e.g., goserelin) are usually used, but antiandrogens (e.g., bicalutamide) may be useful in men who wish to retain their potency, although they result in less prostate shrinkage [25].

The combination of hormone therapy and radiotherapy has been tested in a number of clinical trials with some variation in the way in which hormone therapy was administered (Table 1.1). Based on these findings, there do appear to be several subsets of prostate cancer patients who benefit from hormone therapy plus radiotherapy over radiotherapy alone:

1. Patients with bulky tumors without evidence of distant metastases and Gleason score  $\leq 6$  benefit from short-course neoadjuvant hormone therapy for 4 months (2 months before and 2 months during radiotherapy). It is not known if an LHRH

agonist alone would produce the same benefit as the combination of LHRH agonist and antiandrogen used in RTOG 86-10.

2. Patients with any T stage and no evidence of distant metastases with Gleason score 8 to 10 tumors benefit from long-term hormone therapy (2 to 3 years). Periods of 2 to 3 years have been chosen empirically in most trials, but it is possible that a shorter course may be equally effective; the European Organization for Research and Treatment of Cancer (EORTC) trial 22961 is investigating this possibility.

3. At least some patients with T3 tumors and lower Gleason grade also appear to benefit from long-term hormone therapy, based on a meta-analysis of the RTOG protocols [33], and the EORTC study [29].

The potential benefits of androgen deprivation have to be balanced against toxicity. Most patients experience hot flashes, fatigue, and impotence of varying degrees, which can impact significantly on quality of life. Other toxicities include loss of libido, weight gain, muscle wasting, and changes in texture of hair and skin. Longer-term concerns include the development of osteoporosis and the possibility that low testosterone levels may predispose to cardiovascular disease. There is no evidence yet that long-term hormone therapy increases non-prostate cancer mortality, but this is being investigated; in the meantime, it is sensible to restrict the use of long-term hormone therapy to patient groups in which it has been shown to have an overall survival benefit.

None of the trials in Table 1.1 included a hormone therapy alone arm. Because of this, it is not possible to say with certainty whether the benefits that appear in the patients treated with combined modality therapy are due to the combination of radiotherapy and androgen ablation or the androgen ablation *per se*. The MRC PR02 study [34] did include a hormones-alone arm and randomized 277 patients with T2 to T4 prostate cancer and no bone metastases to orchidectomy alone, radiotherapy alone, or a combination of the two. The study was too small to detect a statistically significant difference in overall survival between the groups, but there was a delay in time to metastasis in patients treated with hormone therapy (with or without radiotherapy). A randomized Medical Research Council study (MRC Prof) is investigating whether radiotherapy contributes anything to long-term hormone therapy in patients with nonmetastatic locally advanced or poor prognosis organ-confined prostate cancer.



**Table 1.1.** Randomized trials of hormone therapy plus radiotherapy

Study	Patient numbers	Patient characteristics	Timing	Outcome
RTOG 85-31 [26,27]	977	T3 or LN positive	Adjuvant goserelin, last week of RT until progression	↑ LC, ↓ DM but OS NS except in Gleason 8 to 10
EORTC [28,29]	415	T1-2 grade 3 or T3-4, any grade (LN negative)	Adjuvant goserelin, first week of RT for 3 years	↑ DFS and OS at 5 years
RTOG 86-10 [30]	471	Bulky T2-4 (+/- LN positive)	Neoadjuvant CAS, 2 months before and 2 months during RT	Overall, ↑ LC, ↓ DM but not in Gleason 7 to 10; OS NS except in Gleason 2 to 6
RTOG 92-02 [31]	1554	T2C-T4, PSA <150 ng/mL	Neoadjuvant CAS for 2 months before +2 months during RT for all patients, then adjuvant goserelin for 2 years or no further treatment	↑ LC, ↑ DFS, ↓ DM but OS NS except in Gleason 8 to 10
RTOG 94-13 [18,32]	1323	T1-4 with risk LN positive >15% or T2C-T4 Gleason ≥6 even if risk LN positive <15%	2 × 2 design: whole pelvic vs. prostate RT; neoadjuvant CAS for 2 months before +2 months CAS for 4 months after RT.	↑ PFS for whole pelvic + neoadjuvant hormones but OS NS during RT or adjuvant

CAS, combined androgen suppression (goserelin + flutamide); DFS, disease-free survival; DM, distant metastases; EORTC, European Organization for Research and Treatment of Cancer; LC, local control; LN, lymph node; NS, nonsignificant; OS, overall survival; PFS, progression free survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group.

## Adjuvant or Salvage Radiotherapy After Surgery

Following radical prostatectomy, patients with positive resection margins, extraprostatic extension (pT3 disease), or seminal vesicle invasion are at increased risk of disease recurrence. There is increasing interest in the role of postoperative radiotherapy in these patients. Radiotherapy (RT) can be administered immediately following prostatectomy (adjuvant RT) or may be postponed until the PSA has risen to a level that is indicative of residual or recurrent prostate cancer (salvage RT). There are no published randomized clinical trials of postprostatectomy radiotherapy, and it is not known whether the results of immediate adjuvant radiotherapy and early salvage radiotherapy are equivalent. Most retrospective studies, however, show that both are generally well tolerated.

Adjuvant radiotherapy is given postoperatively to eradicate possible microscopic residual disease in the periprostatic tissues or adjacent pelvic lymph nodes. It may be considered in men with positive resection margins, extraprostatic extension, or an elevated PSA after surgery. Retrospective studies show that it reduces the local and biochemical recurrence rates in high-risk patients after radical prostatectomy, but there is no evidence yet that it improves survival [35]. Seminal vesicle invasion predicts biochemical failure (rise in PSA) after adjuvant radiotherapy, presumably because it is associated with a high risk of distant metastases. The results of two completed, but yet to be reported, randomized trials of postoperative radiotherapy are awaited in the near future. The Southwest Oncology Group (SWOG) 8794 trial and EORTC 22911 trial have randomized a combined total of over 1300 patients with unfavorable prostate cancer to receive either adjuvant radiotherapy or observation (with salvage radiation on recurrence) following radical prostatectomy.

Salvage radiotherapy is given for patients with biochemical or clinical evidence of recurrent disease following prostatectomy. This approach spares ~40% of patients with high-risk features postprostatectomy who may never have a recurrence. Only patients with disease recurrence confined to the prostatic bed are likely to benefit, and it is therefore important to determine whether a rising PSA represents local recurrence or whether it is an indicator of metastatic disease. Even with local-only recurrence, salvage radiation may not be necessary if life expectancy is short and the risk of symptomatic prostate cancer is low. This is supported by a study of patients with biochemical failure fol-

lowing prostatectomy from Johns Hopkins University, in which the median time from biochemical failure to detection of metastases was 8 years, and the median time from detection of metastases to death was 5 years [36].

Response rates after salvage radiotherapy vary between 10% and 76%, with different patient selection criteria being the most likely explanation for the enormous difference between studies. Factors that predict a favorable outcome after salvage radiotherapy include low preradiation PSA level, low Gleason grade, absence of seminal vesicle involvement, and biochemical failure to be consistent >1 year after prostatectomy [37]. Presalvage PSA appears to be the most consistently reported prognostic variable, and salvage rates are low for patients with pre-RT PSA >2 ng/mL. The increasing sensitivity of PSA testing means that salvage radiotherapy can now be started at much lower PSA levels (0.01 to 0.1 ng/mL) with the expectation that this will yield better results. Consequently, trials using salvage radiotherapy for men with higher PSA levels (including SWOG 8794 and EORTC 22911) may therefore underestimate the efficacy of early salvage radiotherapy compared to adjuvant radiotherapy, and this needs to be considered in their interpretation.

The role of hormone therapy in combination with postoperative radiotherapy is currently unknown. Two RTOG studies currently in progress are addressing this issue: RTOG P-0011 is comparing adjuvant radiotherapy alone versus adjuvant combined modality therapy in high-risk postprostatectomy patients, whereas RTOG 9601 is comparing salvage radiotherapy alone versus combined modality therapy in patients with a rising PSA (>0.2 ng/mL and <4 ng/mL) after radical prostatectomy.

## Conclusion

Current evidence suggests that radiotherapy is as effective as other curative modalities for prostate cancer. As well as the need for more mature data from high-dose, conformal studies, the ongoing randomized trials will better define its role. The optimum duration of hormone therapy is still unclear, and the patient population that most benefits from combined hormone therapy plus radiotherapy needs to be better defined. The next 5 to 10 years will yield some important data in clarifying these and other issues.

## Controversies and Outstanding Issues

1. Does radical radiotherapy prevent progression to metastatic disease?
2. Does increasing the radiotherapy treatment dose increase local control rates?

## References

1. Holmberg L, Bill-Axelsson A, Helgesen F, et al. A randomised trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002;347:781–789.
2. Paulson DE, Lin GH, Hinshaw W, et al. Radical surgery versus radiotherapy for adenocarcinoma of the prostate. *J Urol* 1982;128:502–504.
3. D'Amico AV, Whittington R, Malcovic SB, et al. Biochemical outcome after radical prostatectomy or external beam radiation therapy for patients with clinically localised prostate carcinoma in the prostate specific antigen era. *Cancer* 2002;95:281–286.
4. Kupelian PA, Elshaikh M, Reddy CA, et al. Comparison of the efficacy of local therapies for localised prostate cancer in the prostate-specific antigen era: a large single-institution experience with radical prostatectomy and external-beam radiotherapy. *J Clin Oncol* 2002; 20:3376–3385.
5. Wilt TJ, Brawer MK. The prostate cancer intervention versus observation trial; a randomised trial comparing radical prostatectomy versus expectant management for the treatment of clinically localised prostate cancer. *J Urol* 1994;152:1910–1914.
6. Madalinska JB, Essink-Bot M-L, de Koning HJ, et al. Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localised prostate cancer. *J Clin Oncol* 2001;19: 1619–1628.
7. Seddon B, Bidmead M, Wilson J, et al. Target volume definition in conformal radiotherapy for prostate cancer: quality assurance in the MRC RT-01 trial. *Radiother Oncol* 2000;56:73–83.
8. Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;43:1095–1101.
9. Livsey JE, Cowan RA, Wylie JP, et al. Hypofractionated conformal radiotherapy in carcinoma of the prostate: five-year outcome analysis. *Int J Radiat Oncol Biol Phys* 2003;57:1254–1259.
10. Lukka H, Hayter C, Warde P, et al. A randomised trial comparing two fractionation schedules for patients with localised prostate cancer. *Int J Radiat Oncol Biol Phys* 2003;57(suppl).

11. Zelefsky MJ, Fuks Z, Hunt M, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localised prostate cancer. *J Urol* 2001;166:876–881.
12. Kuban DA, Thames HD, Levy LB, et al. Long- term multi-institutional analysis of stage T1-T2 prostate cancer treated with radiotherapy in the PSA era. *Int J Radiat Oncol Biol Phys* 2003;57:915–928.
13. Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999;353:267–272.
14. Pollack A, Zagars GK, Starkschall G, et al. Prostate cancer radiation dose response: results of the M.D. Anderson Phase III randomised trial. *Int J Radiat Oncol Biol Phys* 2002;53:1097–1105.
15. Ryu JK, Winter K, Michalski JM. Interim report of toxicity from 3D conformal radiation therapy (3D-CRT) for prostate cancer on 3DOG/RTOG 9406, level III (79.2 Gy). *Int J Radiat Oncol Biol Phys* 2002;54:1036–1046.
16. Zelefsky MJ, Fuks Z, Hunt M, et al. High- dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002;53: 1111–1116.
17. Kupelian PA, Reddy CA, Carlson TP, et al. Preliminary observations on biochemical relapse-free survival rates after short-course intensity- modulated radiotherapy (70 Gy at 2.5 Gy/fraction) for localised prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;53: 904–912.
18. Roach M III, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003;21:1904–1911.
19. Nutting CM, Convery DJ, Cosgrove VP, et al. Reduction of small and large bowel irradiation using an optimised intensity-modulated pelvic radiotherapy technique in patients with prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;48:649–656.
20. Merrick GS, Butler WM, Galbreath RW, et al. Five-year biochemical outcome following permanent interstitial brachytherapy for clinical T1-T3 prostate cancer. *Int J Radiat Oncol Biol Phys* 2001;51:41–48.
21. Grimm PD, Blasko JC, Sylvester JE, et al. 10-year biochemical (prostate-specific antigen) control of prostate cancer with <sup>125</sup>I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51:31–40.
22. Martinez AA, Gustafson G, Gonzalez J, et al. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavourable prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;53: 316–327.
23. Yoshioka Y, Nose T, Yoshida K, et al. High-dose-rate brachytherapy as monotherapy for localised prostate cancer: a retrospective analy-

- sis with special focus on tolerance and chronic toxicity. *Int J Radiat Oncol Biol Phys* 2003;56:213–220.
24. Zelefsky MJ, Leibel SA, Burman CM, et al. Neoadjuvant hormonal therapy improves the therapeutic ratio in patients with bulky prostatic cancer treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 1994;29:755–761.
  25. Henderson A, Langley SEM, Laing RW. Is bicalutamide equivalent to goserelin for prostate volume reduction before radiation therapy? A prospective, observational study. *Clin Oncol* 2003;15: 318–321.
  26. Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavourable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. *J Clin Oncol* 1997;15:1013–1021.
  27. Lawton CA, Winter K, Murray K, et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavourable prognosis carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;49:937–946.
  28. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.
  29. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002;360:103–108.
  30. Pilepich MV, Winter K, John MJ, et al. Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;50:1243–1252.
  31. Hanks GE, Lu J, Machtay M, et al. RTOG protocol 92-02: a phase III trial of the use of long-term androgen suppression following neoadjuvant hormonal cytorreduction and radiotherapy in locally advanced carcinoma of the prostate. *Proc Annu Meet Am Soc Clin Oncol* 2000;19:1284.
  32. Roach M III, Lu JD, Lawton C, et al. A phase III trial comparing whole-pelvic (WP) to prostate only (PO) radiotherapy and neoadjuvant to adjuvant total androgen suppression (TAS): preliminary analysis of RTOG 9413. *Int J Radiat Oncol Biol Phys* 2001;51(suppl 1).
  33. Roach M III, Lu J, Pilepich MV, et al. Predicting long-term survival, and the need for hormonal therapy: a meta-analysis of RTOG prostate cancer trials. *Int J Radiat Oncol Biol Phys* 2000;47:617–627.
  34. Fellows GJ, Clark PB, Beynon LL, et al. Treatment of advanced localised prostatic cancer by orchidectomy, radiotherapy or combined treatment. A Medical Research Council Study. *Urological*

- Cancer Working Party–Subgroup on Prostatic Cancer. *Br J Urol* 1992; 70:304–309.
35. Catton C, Gospodarowicz M, Warde P, et al. Adjuvant and salvage radiation therapy after radical prostatectomy for adenocarcinoma of the prostate. *Radiother Oncol* 2001;59:51–60.
  36. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591–1597.
  37. Parker C, Warde P, Catton C. Salvage radiotherapy for PSA failure after radical prostatectomy. *Radiother Oncol* 2001;61:107–116.



<http://www.springer.com/978-1-84628-464-9>

Urological Cancers in Clinical Practice

Waxman, J. (Ed.)

2007, XII, 275 p., Softcover

ISBN: 978-1-84628-464-9