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Technological advances in radiotherapy for the treatment of localised prostate cancer

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Abstract

There is good evidence that radiation dose escalation in localised prostate cancer is associated with increased cell kill. The traditional two-dimensional (2D) technique of treatment planning and delivery is limited by normal tissue toxicity, such that the dose that can be safely delivered to the prostate by external beam radiotherapy is 65–70 Gy. Several technological advances over the last 20 years have enhanced the precision of external beam radiotherapy (EBRT), and have resulted in improved outcomes. The three-dimensional conformal radiotherapy (3D-CRT) approach reduces the dose-limiting late side-effect of proctitis and has allowed for dose escalation to the whole prostate to 78 Gy. More recently, intensity modulated radiotherapy (IMRT), an advanced form of conformal therapy, has resulted in reduced rectal toxicity when using doses greater than 80 Gy. In addition, IMRT can potentially escalate the dose to specific parts of the prostate where there are resistant subpopulations of tumour clonogens, or can be used to extend the high-dose region to pelvic lymph nodes. The addition of androgen deprivation to conventional radiotherapy has an impact on survival and local control. Initial hormone therapy causes cytoreduction of the prostate cancer allowing for a reduction in radiotherapy volume as well as an additive effect on cell kill. Long-term adjuvant androgen deprivation has been shown to improve overall survival in more advanced tumours. Prostate brachytherapy is now a recognised treatment for those with low-risk disease. It achieves similar long-term outcome to other treatment modalities. Brachytherapy can be used as monotherapy for localised disease, or as boost treatment following conventional EBRT for locally advanced disease. New techniques are available to improve the precision of both target definition and treatment verification. This so-called image-guided radiotherapy will help to enhance the accuracy of dose delivery by correcting both for inter-fraction positional variation and for intra-fraction movement of the prostate in real-time and will allow for tighter tumour margins and avoidance of normal tissues, thereby enhancing the safety of treatment.

Keywords: Prostate cancer; Radiotherapy

1. Introduction

External beam radiotherapy (EBRT) is widely accepted as a curative treatment modality for localised prostate cancer. The introduction of cobalt machines and linear accelerators [1] 50 years ago allowed for the use of highly penetrating megavoltage beams which were able to deliver tumoricidal doses to the target volume whilst sparing damage to the skin and normal surrounding tissue. This improvement in technology helped to change the concept of radiotherapy, from palliation of advanced prostate cancer to a curative approach for localised disease [2]. Fundamental to this therapeutic philosophy was the need to deliver an adequate dose

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to eradicate the tumour whilst avoiding toxicity to adjacent organs, i.e., bowel and bladder. The tolerance of these structures to the amount of radiotherapy received governed the dose that could be safely applied.

Over the last 20 years advanced imaging technology together with sophisticated radiation dosimetry has resulted in the development and implementation of three-dimensional conformal radiotherapy (3D-CRT), and, more recently, Intensity Modulated Radiotherapy (IMRT). These sophisticated techniques have improved the conformality of the treatment delivery and improved clinical outcomes with regards to the delivery of external beam radiotherapy. Parallel with this, the development of transrectal ultrasound and sophisticated computer planning and dosimetry have contributed to the resurgence of prostate brachytherapy as a viable option for the treatment of localised prostate cancer. This article will review the technological advances that have taken place in these areas and assess the impact on clinical outcome, as well as looking at newer developments that are under investigation.

2. Conventional radiotherapy

Historically, the localisation of megavoltage radiotherapy for localised prostate cancer was based on information obtained from plain film simulator techniques [3]. Anatomical landmarks included the location of the pubic bone, and identification of the bladder and rectum using contrast media inserted via a urinary catheter, and rectal examination respectively. Due to inability to identify the tumour precisely, large safety margins were needed. Field sizes varied between 6×6 and 8×8 cm, and could be applied with a rotational arc technique. Although this approach provided satisfactory coverage for small T1 and T2a tumours [4], retrospective reconstruction with computerised tomographic (CT) imaging has shown that even a large 8×8 cm field size failed to cover adequately most bulky or locally advanced tumours, especially when the seminal vesicles needed to be within the target volume [5,6]. A major disadvantage of the rotational technique was that it did not allow for shaped blocking to shield normal tissues. Hence, a large volume of bladder and rectum received the same dose as the tumour. Thus, this technique, when administered with traditional two-dimensional (2D) treatment planning, limited the dose that could safely be given to between 65 and 70 Gy in 2 Gy/fraction. It is important to appreciate that many of the available long-term outcome data for radiation in prostate cancer are collated from patients who were treated in the 1970s with this technique [7,8].

With the advent of CT, which helped to define the geometry and location of the prostate and seminal vesicles more precisely, conventional EBRT is now based on CT-assisted planning [9]. Patients are treated in the supine position and are asked to empty their bowel before CT simulation and treatment. A three-field approach is commonly used (anterior and opposed lateral portals using 8–20 MV photons). The cross-section of each beam can be blocked using individualised cerrobend alloy blocks in an attempt to exclude bladder, rectum and small bowel from the treatment field. Using this so-called 2D planning, treatment can be given via a 2-phase technique, initially treating the whole pelvis to 45–50 Gy to cover regional nodes, then boosting the prostate and seminal vesicles (surrounded by a 1–2 cm margin) with a further 20 Gy to a total dose of 65–70 Gy [9]. Although the true rates of local relapse after conventional EBRT remain uncertain, disease recurrence after radical treatment is common. Long-term follow-up studies since the introduction of prostate-specific antigen (PSA) measurement as a surrogate end-point after radiotherapy, have shown actuarial PSA failure rates of 29% for T1 tumours, 46% for T2a, and as high as 80% for T2b/c, T3, or T4 cancers [10,11]. Lavèrdiere and colleagues [12] looked at biopsy-proven local recurrences following radiotherapy and found that 65% of those with T2–T3 tumours that were treated with 65 Gy had a positive biopsy at 24 months. These figures indicated that conventional EBRT techniques were not adequate to eradicate localised disease, especially those with locally advanced tumours, and provided the impetus for further improvement in dose delivery and technique.

3. Three-dimensional conformal radiotherapy

This form of radiation treatment involves the shaping of individual beams to conform the high radiation dose contour to the shape of the tumour volume, thus reduce the volumes of normal tissues exposed to high-dose levels. It provides an approach to partially address the issue of increasing rectal toxicity with dose escalation. During the past decade, the increased availability of CT scanners and the development of sophisticated three-dimensional (3D) planning and delivery systems have made the clinical use of 3D-CRT practical.

3D-CRT allows a 3D and volumetric appreciation of the target volume; treatment planning is based on the ability to define anatomically each sub-volume within the entire 3D space of irradiated tissues and to precisely calculate the dose delivered at each point. This requires large numbers of dose computation points, and its implementation depends on the availability of efficient computer algorithms and sophisticated computer hardware [13]. Treatment planning begins with the acquisition of anatomical data from a planning volumetric CT scan. Slices are taken at 2–5 mm intervals with the patient in the treatment position. On each slice of the CT scan, the target volume and organs at risk (bowel and femoral heads) are defined and contoured. CT

software allows the creation of a Beam's Eye View (BEV) in which the target volume is viewed as if the observer's eye is placed at the source of the radiation (in the head of the machine). This 3D visualisation allows the radiotherapist to choose radiation beam shapes to cover the tumour and minimise exposure of normal structures [14] (Fig. 1). Typically, 3D-CRT employs multiple treatment fields (three–eight). Treating this many uniquely shaped fields is achieved most efficiently and accurately with a multi-leaf collimator (MLC). This device is located within the head of the linear accelerator and is made up of many small tungsten leaves (1 cm projection at the radiotherapy linear accelerator isocentre) that are driven by independent motors to create the desired shape of radiation field [15]. Thus, the shape of the radiation field can be customised for each treatment field depending on the shape of the PTV as seen from the BEV. These devices avoid the need for the heavy lead blocks that were used in the past.

Whilst long-term results are awaited, there is good clinical evidence to support 3D-CRT in routine clinical practice. Hanks and colleagues [16] found a 34% grade

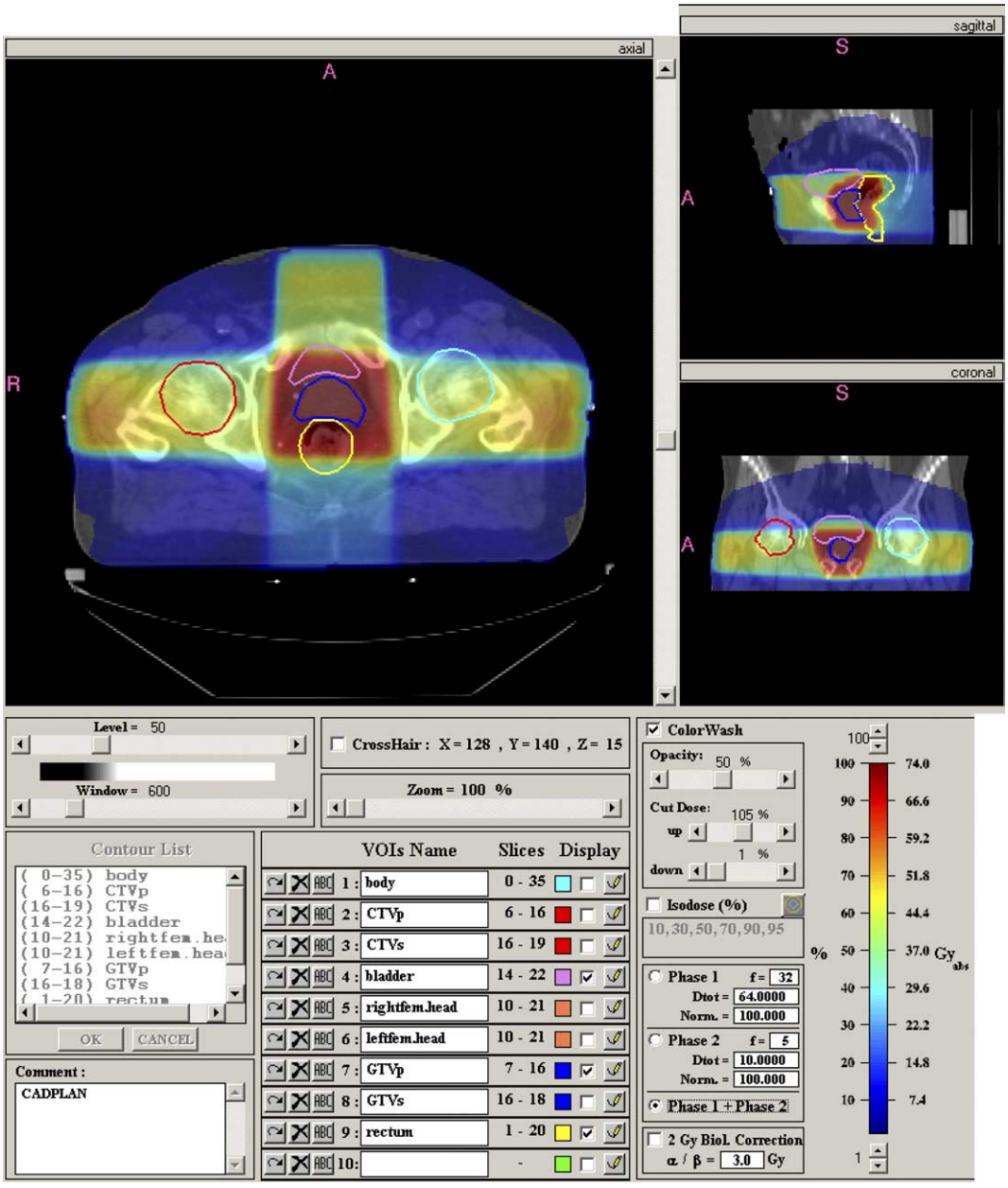

Fig. 1. Three-dimensional conformal radiotherapy (3D-CRT) plan-showing the isodose distribution for the prostate gland and surrounding structures. The 3D analysis shows the extent of the high-dose area with regards to covering the prostate and allows an appreciation for the volume of the rectum and bowel within the high-dose area.

2 gastrointestinal (GI) and genitourinary (GU) acute toxicity compared with 57% reported in those treated with standard radiotherapy. Similarly, there is evidence for reduced late rectal toxicity. A randomised phase three trial conducted at the Royal Marsden Hospital [17] compared conformal with conventional radiotherapy using a standard dose of 64 Gy and showed a significant reduction in the dose-limiting side-effect of proctitis (8% compared with 18%). Analysis of dose volume histograms in patients receiving greater than 75.6 Gy has shown that rectal wall volume was significantly higher at each dose level in those suffering the toxicity of rectal bleeding ($P < 0.05$) [18].

4. Dose escalation and limitations of conventional radiotherapy

The recognition that the radiation dose is an independent determinant of biochemical outcome has been reported in several retrospective, sequential, prospective and now randomised trials [19]. Initial studies in the pre-PSA era supported the notion that local tumour control is directly dose-related and levels greater than 70 Gy were needed for controlling prostate cancer. Hanks and colleagues [20] reported the local outcome of 624 patients with T3 prostate cancer from the American College of Radiology Patterns of Care Study. The 7-year clinical local recurrence rates based on digital rectal examination were 36% for patients receiving 60–64.9 Gy compared with 24% for those treated with 70 Gy or higher. More recently, a retrospective analysis from the Radiotherapy and Oncology Group (RTOG), which included 1465 men treated between 1975 and 1992, found that men with high-grade cancers who received higher radiation doses (>66 *vs.* <66 Gy) had a 27% reduction in overall mortality [21].

A randomised trial conducted by the M.D. Anderson Cancer Centre provided confirmation that dose escalation does improve biochemical control rates [22]. This trial, conducted between 1993 and 1998, recruited over 300 men with localised prostate cancer (T1–T3) who received radical conformal radiotherapy to the prostate and seminal vesicles and were randomised to either conventional dose (70 Gy) or high-dose (78 Gy). With a median follow-up of 5 years, the higher dose improved the biochemical control rates from 64% to 70% ($p = 0.03$). However, this was at the cost of increased bowel toxicity. The actuarial risk of $\geqslant$grade 2 rectal toxicity at 6 years was 12% and 26% for the 70 and 78 Gy arms, respectively, ($p = 0.001$). Subgroup analysis suggested that the benefit of dose escalation was greater for those with a pre-treatment PSA > 10 ng/ml.

Whilst this study provided good evidence that dose escalation does improve the outcome of prostate radiotherapy, it does highlight some areas of contention. First, dose escalation comes at the cost of increased toxicity. This confirms the experience of earlier studies where doses greater than 70 Gy almost doubled the risk of grade 3–4 bowel and bladder complications [23]. Secondly, the group of patients who stand to benefit most has not been clearly defined. In low-risk patients, for whom conventional doses would have been sufficient, dose escalation may just increase the risk of toxicity with no overall benefit. It is also important to note that while the effect of radiation dose escalation on biochemical endpoints is very encouraging, there is less evidence that this translates into an impact on overall survival.

There are many ongoing phase three studies of dose escalation based on 3D-CRT to reduce toxicity and improve clinical outcomes. For example, a phase three pilot study conducted by the Royal Marsden Hospital, has looked at the issue of dose escalation with respect to the safety margins needed around the tumour volume. One hundred and twenty six men with localised prostate cancer underwent a 2×2 randomisation between 64 and 74 Gy following neoadjuvant androgen suppression and between a PTV margin of either 1 or 1.5 cm around the tumour. After a median follow-up of 4.25 years, there was a non-significant improvement in biochemical control for the 74 Gy group (71% *vs.* 59%). There was no difference in disease control between the 1 and 1.5 cm margin groups. However, the reduction in the PTV margin by 0.5 cms resulted in reduced late bowel toxicity, without compromising local control [24].

In the United Kingdom (UK), the Medical Research Council (MRC) RTO1 trial is comparing doses of 64 and 74 Gy in men receiving neoadjuvant androgen suppression in addition to radiation, and completed recruitment of over 850 patients in 2001 [25].

5. Intensity modulated radiotherapy (IMRT)

IMRT is a technological advance in conformal radiotherapy in which there is variation of the quantity of radiation (fluence) across the beam. The potential advantages include more control of the shape of the high-dose envelope, for example, to include a concavity around an adjacent critical normal tissue, and also the ability to deliver heterogeneous doses to boost the dose to subtargets in the tumour volume [26].

It requires two additional steps beyond 3D-CRT – inverse treatment planning and intensity modulation of the beam. Normally, treatment planning for target volumes that are convex or are separated from normal tissues is fairly straightforward. Using experience, dosimetrists can estimate and then adjust beam numbers and relative weights until suitable distributions are achieved. This forward planning will not work for IMRT, due to the large number of potential

combinations of field intensities. Instead, inverse dose planning is used in which the required dose distribution is defined first within a set of dose constraints (Table 1). Using this information, the planning computer then designs the optimal beam profiles necessary to produce their distribution [27]. Inverse planning allows the input of a desired high-dose to the target volume and a desired low-dose to adjacent sensitive structures, while informing the system of levels of compromise that should be made if a conflict arises between the two goals.

There are a variety of methods to deliver modulated beam intensity. Most use some form of MLC, (already incorporated into modern linear accelerators) whose leaves can be individually partitioned creating beam apertures of various dimensions (Fig. 2). The MLC can create intensity modulated fields in different ways. Two possibilities are in clinical use. Firstly, the MLC leaf pairs can be programmed to move independently of each other during the few minutes of each treatment whilst the beam is continuously switched on. This is termed Dynamic MLC. Secondly, the MLC can be used to construct a sequential series of different shaped conformal fields. Areas of intermediate dose are created if they are blocked out by the MLC for some of the fields. This technique is termed Step and Shoot MLC [28] (Fig. 3).

Fig. 2. A varian multi-leaf collimator (MLC), showing a complicated shape that can be created with the bank of leaf pairs. The distance between each pair can be varied during dynamic IMRT with the beam continuously on.

Table 1
IMRT prostate and pelvic node plan assessment – inverse planning – setting dose constraints[a]

Target structures	Volume constraint	Dose required	Dose achieved
Prostate PTV	99%	90% (63.0 Gy)	
	95%	95% (66.5 Gy)	
	⩽5%	105% (73.5 Gy)	
Nodal PTV	99%	90% (Gy)	
	95%	95% (Gy)	
	50%	100% (Gy)	
Risk structures	**Dose**	**Volume restraint for the development of ⩽ grade 1 (CTC) toxicity**	**Volume achieved**
Bowel	45 Gy	158 cc	
	50 Gy	110 cc	
	55 Gy	28 cc	
	60 Gy	6.0 cc	
	65 Gy	0.0 cc	
Bladder	50 Gy	50%	
	60 Gy	25%	
	70 Gy	5%	
Rectum	65 Gy	30%	
	70 Gy	15%	
	75 Gy	3%	
	Volume	**Dose constraint**	**Dose achieved**
	95%	45 Gy	

[a] The table shows an example of the planning sheet used at the Royal Marsden Hospital for IMRT inverse dose planning. In the first part of the Table, the dose required for volumes within the prostate and nodal target volumes are pre-defined. In the second part of the Table, volume restraints are set for each dose level that the organs at risk receive. The doses and volumes actually achieved for each of the parameters by the IMRT plan are then inserted to complete the table. PTV – planned target volume, volume constraint – the volume of the PTV that receives the specified dose, volume restraint – the maximum volume of the PTV permissible for a specified dose, dose constraint – the maximum dose permissible for a certain volume of the PTV.

There is now good clinical evidence to confirm that IMRT can reduce acute and late occurring toxicities, and thereby serve as a tool for dose escalation. Zelefsky and colleagues [29] followed a series of 772 patients for a median of 24 months who were treated with a dose of either 81 Gy or more. This resulted in ⩾grade 2 toxicity of just 4% at three years. The three-year actuarial PSA relapse-free survival rates among patients with low-, medium- and high-risk for biochemical relapse treated with 81 Gy were 93%, 84% and 81%, respectively. Within this study, the authors planned 20 patients with both 3D-CRT and IMRT for comparative analysis. Histogram analysis revealed that IMRT planning resulted in a larger volume of targeted malignant tissue receiving the prescribed dose relative to 3D-CRT [29].

3D conformal therapy has allowed dose escalation to the whole prostate, but IMRT can be used to escalate the dose to other targets also, such as the pelvic lymph nodes (Fig. 4) and intra-prostatic tumour nodules [30]. The latter can be localised using new imaging that has

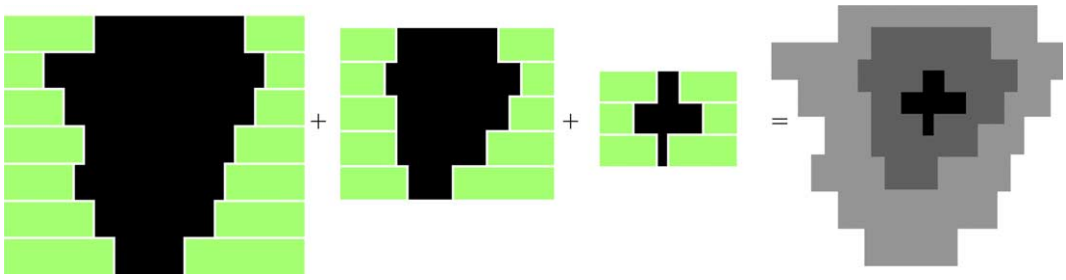

Fig. 3. Step and shoot intensity modulated radiotherapy (IMRT) delivery. Each segment, shaped by the MLCs, contributes towards the total treatment, which can be altered to create the desired fluence profile.

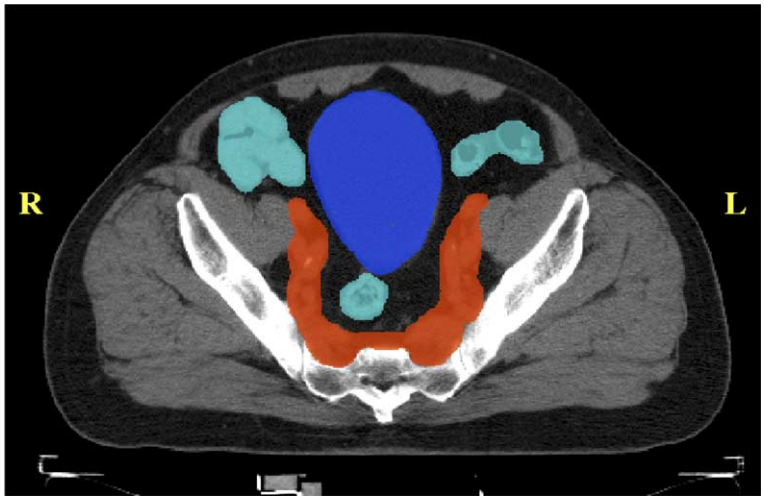

Fig. 4. The outlined nodal volume (brown) shows the typical horseshoe appearance at the level of S2. The nodal groups within this area include the pre-sacral nodes posteriorly, and the external iliac and hypogastric and obturator nodes laterally. Note the bowel (green) and bladder (blue) within the central concavity. This arrangement is ideal for IMRT.

the potential to define tumour foci of differing radiosensitivities [31].

The body of clinical evidence for IMRT remains limited. IMRT is time-consuming, expensive and complex, and may not offer an advantage over more conventional techniques for all patients. Issues that need to be addressed by longer term follow-up and future research should include clinical outcome data, the establishment and refinement of patient selection criteria, optimising treatment planning and delivery, and cost analysis.

6. Combining external beam radiotherapy with androgen deprivation

The inhibitory effect of androgen deprivation on the growth and proliferation of androgen-dependant prostate cancer cells is well recognised. The combination of androgen deprivation with external beam irradiation provides a way of increasing the therapeutic ratio, but without increasing radiation toxicity. The first convincing demonstration of an overall survival benefit for adjuvant androgen-deprivation in men receiving radical radiotherapy for prostate cancer was given in the report of the European Organisation for Research and Treatment of Cancer (EORTC) trial by Bolla and colleagues [32]. In this trial, 415 men with T3/4 tumours or poorly differentiated T1 and T2 tumours were randomised between radiotherapy alone to the prostate and pelvis or to a combined modality treatment with an luteinising hormone releasing hormone (LHRH) agonist commenced at the beginning of radiotherapy and continued for a period of three years. At a median follow-up of 45 months, there was an improvement in local disease control (97% *vs.* 77%), disease-free survival (85% *vs.* 48%), and also in overall survival (79% *vs.* 52%, $p = 0.001$) in favour of the combined modality treatment. Since then, there have been several important randomised trials looking at the optimal timing of hormonal treatment.

6.1. Neo-adjuvant hormonal therapy

The potential attraction of administering androgen deprivation prior to radiotherapy is that it might not

only improve tumour control *via* an additive effect on cell kill, but also allows for a reduction in radiotherapy target volume by 20–50% [33,34]. The largest phase three trial was conducted by the RTOG in 471 patients with T2–T4 primary tumours who were treated with combined androgen blockade for 2 months before and continuing during radiotherapy, compared with a group treated with radiotherapy alone. With a median follow-up of 8.7 years, there was a non-significant trend towards improved overall survival for the group receiving both radiation and hormone therapy (8-year survival: 53% *vs*. 44%, $P = 0.10$). A statistically significant survival advantage was seen in the subgroup of 129 cases with Gleason 2–6 disease, in whom the 8-year survival was 70% *vs*. 52% for those receiving radiation alone [35].

This study is in keeping with a more recent prospective randomised trial by Laverdiere and colleagues [36] who recruited 481 patients with T2 and T3 localised prostate cancer into two successive trials. In the first trial, 161 patients were randomised to receive EBRT alone or in combination with either three or ten months of AS starting at three months prior to EBRT. In the second part of the study, 325 patients were then randomised to either 5 or 10 months of AS, again starting at 3 months prior to EBRT. At a median follow-up of five years for the first study, there was improved local control in favour of neoadjuvant AS. In the second study, there was no significant difference between 5 and 10 months of androgen suppression. Although confirmatory data from other phase three trials are still awaited, it is now widely accepted that those who receive radical radiotherapy for locally advanced disease should have at least short-term neoadjuvant hormone therapy.

6.2. Adjuvant hormonal therapy

The rationale for adjuvant treatment is to eradicate residual tumour clonogens that remain after radiotherapy, either within the prostate or at distant metastatic sites. The question is whether there is an additional benefit for continuing long-term hormonal treatment after radiotherapy. This issue was addressed by the RTOG 92-02 and 85-31 trials. The RTOG 92-02 trial recruited over 1500 men with locally advanced disease who received radical radiotherapy with 4 months of neoadjuvant total androgen suppression and were randomly allocated to receive an additional 2 years of adjuvant goserelin or to observation [37]. Overall, the duration of adjuvant hormone therapy had no effect on survival. Five-year overall survival was 78% *vs*. 79% for long-term and short-term adjuvant therapy, respectively. However, subgroup analysis of patients with Gleason 8–10 disease demonstrated a significant survival advantage for long-term adjuvant therapy with a 5-year overall survival of 80% *vs*. 69% ($P = 0.02$). These results are in accordance with long-term data from the RTOG 85-31 trial whose results have recently been updated [38]. This trial randomised 977 patients with locally advanced disease or post-operative cases with positive resection margins to either radiotherapy alone or adjuvant hormones. Androgen suppression started at the end of radiotherapy until disease progression with up to 11 years of follow-up. Patients who received hormones had improvement in terms of local control (30% *vs*. 50% local failure), distant metastases (25% *vs*. 40%) and overall survival (53% *vs*. 35% $P = 0.043$). As seen with RTOG 92-02, subset analysis showed that those with Gleason score tumours 2–6 did not derive any significant benefit with adjuvant hormones.

In an overview of RTOG studies, four prognostic groupings were identified. The conclusion was that in patients in group 2, (mainly those with bulky T2 or with T3 and moderately differentiated tumours), initial androgen suppression led to a survival benefit. For those in group three or four (>T3, or poorly differentiated), there was a survival advantage for long-term adjuvant hormone therapy [39].

Long-term adjuvant treatment is not without its risks. It has previously been suspected that long-term LHRH analogue therapy could be linked with an excess of non-prostate cancer deaths [40]. This was also highlighted in the RTOG 92-02 trial [37] where in those men with Gleason Score less than 7, there was actually a trend to survival detriment. Although 5-year disease-specific survival for this group was marginally improved by approximately 1% (estimated at 95.8% *vs*. 95%), this was outweighed by a 2% increased risk of death from causes other than prostate cancer (15.6% *vs*. 13.6%). The mechanism of any such effect is not known, but low testosterone levels have been associated with a range of risk factors for cardiovascular disease, [41] and LHRH therapy has been linked with increased insulin resistance and arterial stiffness [42].

In a recent trial, D'Amico [43] randomised 206 patients with localised prostate cancer (with Gleason Scores of at least 7, and PSA > 10) to EBRT alone or in combination with 6 months of androgen suppression (starting 2 months prior to radiotherapy). After nearly 4.5 years of follow-up, the study showed that men who received the combination treatment had improved survival rates compared with those who received radiation alone (88% *vs*. 78%). The importance of this trial is that it demonstrates that the addition of AS to radiotherapy confers an overall survival advantage. However, the question of whether long-term AS can provide an additional survival benefit over short-term AS for those with locally advanced, or high-grade localised tumours remains unanswered. This is the subject of a recently completed, but not yet reported, European randomised study comparing 6 months with 3 years of AS.

7. Prostate brachytherapy

Brachytherapy seeks to maximise the therapeutic ratio by exploiting the inverse square law, which results in a sharp fall off in dose outside of the prostate and hence reduces the effects of radiation on normal surrounding tissues. Also the use of continuous low-dose rate radiotherapy which may confer radiobiological benefits [44].

Prostate brachytherapy has its origins in the early part of the last century; in 1914, Pasteau reported a technique whereby radium capsules were inserted transurethrally into the prostate [45]. In the early 1970s, a technique was popularised by Whitmore and colleagues who inserted the seeds via an open laparotomy using a retropubic freehand approach [46]. This procedure was frequently associated with heavy bleeding, which often obscured the prostate leading to inaccurate placement of the seeds (Fig. 5). However, in the small group of patients who achieved a satisfactory seed distribution, long-term control was achievable. As technology for medical imaging improved, effective means of planning and monitoring the placement of the seeds were developed and led to a renewed interest in the technique.

Brachytherapy can be delivered using either permanent seed implants- a form of interstitial low-dose rate treatment, or, more recently, with a high-dose rate (HDR), where the seeds are delivered via an afterloading technique and remain in the prostate for approximately 5–8 min. Permanent seed implantation has been the traditional approach to treating localised disease, whilst HDR-brachytherapy has mainly been used as an alternative to conformal EBRT in boosting the prostate following EBRT, but is now increasing in popularity for use as monotherapy in selected cases.

7.1. Permanent seed implantation

This is performed using real-time rectal ultrasound; seeds are introduced transperineally via needles passing through a metal template secured to the perineum [47]. Iodine-125 and Palladium-103 are the two main radioisotopes used in the seed implants. Some brachytherapists

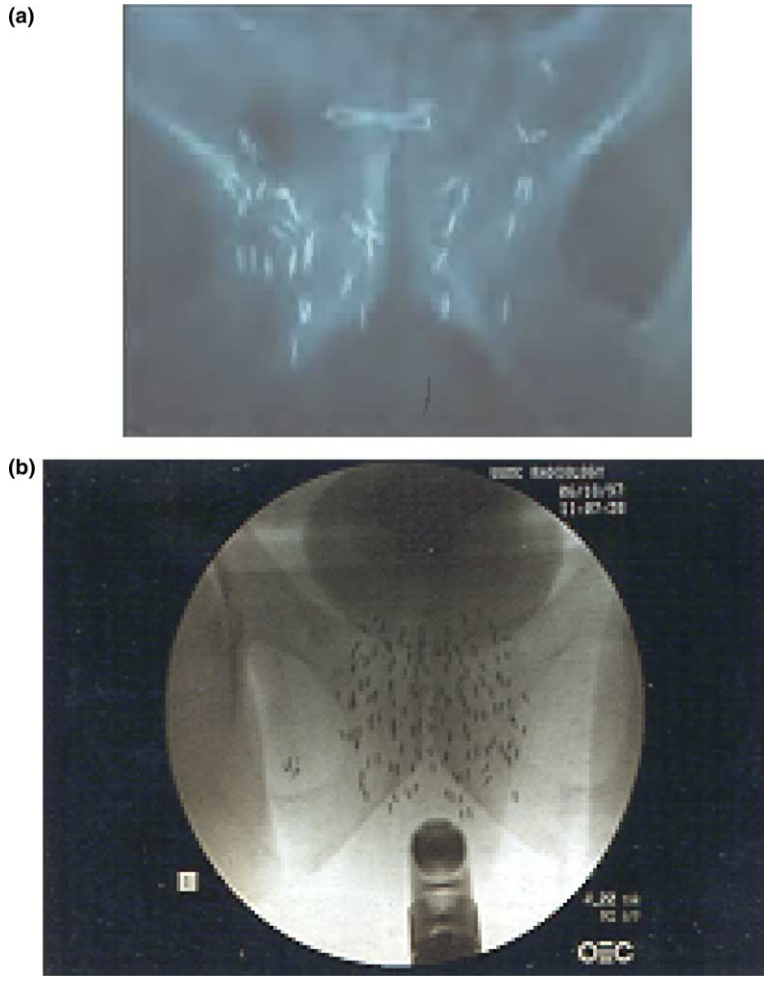

Fig. 5. (a) Placement of brachytherapy seeds via traditional freehand retropubic approach. (b) Placement of seeds via modern transperineal approach using transrectal ultrasound (seeds identified using fluoroscopy).

decide which isotope to use based on the aggressiveness of the tumour. Iodine-125 has a slower dose rate and is used on slower growing tumours. Palladium-103 has a higher dose rate and is used on faster growing tumours [48,49]. However, this idea has not been verified in formal studies. The shorter half life of Palladium-103 may help to reduce the duration of acute urinary toxicity when compared with Iodine-125 [50].

Prior to the implant, a transrectal ultrasound is performed to determine the volume of the prostate and its relationship to the pubic arch (implantation may not be possible if a significant proportion of the prostate lies behind the pubic ramus). The ultrasound maps the position of the prostate in sequential slices akin to CT imaging methods, onto the implant template image which is superimposed on the scans. A pre-plan calculation is done to determine in which holes of the template the needles need to be inserted, and how many seeds to deposit through each needle to adequately irradiate the prostate [47]. The number of seeds used depends on the size of the prostate, but typically most implants require 60–120 seeds. The implant is then conducted usually a few weeks after the initial volume study, placing the seeds under ultrasound guidance (Fig. 6). The seeds are placed predominantly in the periphery of the gland in order to reduce the urethral dose. A typical dose used is 145 Gy prescribed to the 100% isodose – The Minimum Peripheral Dose [51]. A CT scan is conducted 4–6 weeks after the implant for post-implant dosimetry assessment.

7.2. High-dose rate brachytherapy

High-dose rate brachytherapy uses the radioisotope Iridium-192, which can be formed into radioactive pellets (1 mm × 3 mm). These sources are housed in a computer-guided afterloader, and delivered to the prostate via interstitial catheters that are inserted transperineally, using transrectal ultrasound in a manner similar to permanent seed implants. The source travels through each catheter in 5 mm steps-dwell positions. The distribution of radiation and dose is determined by which dwell positions the source stops at and the length of time it dwells there. Due to the high radioactivity of the iridium, the treatment time is in minutes, following which the source retracts into the afterloader.

This technique has been employed mainly as a boost treatment to the prostate following EBRT. It offers distinct advantages over using a boost with conformal EBRT in that it leads to a more precise dose delivery system overcoming errors associated with internal prostate motion and uncertainties associated with daily dose delivery of EBRT [52].

The doses used vary widely across Europe and the United States and a consensus on dose fractionation is lacking. The dose prescription used at the Mount Vernon Hospital is two fractions of 0.85 Gy daily following 35.7 Gy/13f of EBRT. Assuming a relatively low alpha/beta ratio of 1.5 for prostate cancer tumour control, this equates to a BED of 214.4 compared with 150 for a radical course of EBRT alone [53]. Similarly, there is considerable variation in the dose used in monotherapy. For example, the Beaumont Hospital uses 36 Gy in four fractions given twice daily over two days [54].

7.3. Comparison of HDR and LDR

One of the major drawbacks of permanent seed implants is that once the sources are placed in the patient

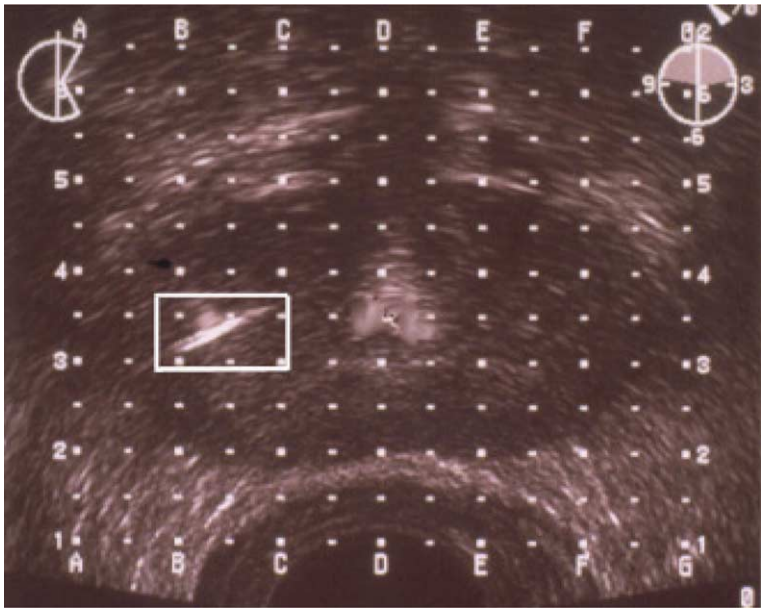

Fig. 6. Placement of the seed under ultrasound guidance. The seed produces a dense hyperechoic signal on ultrasound. The overlying electronic template helps to define the seed placement.

there is little that can be done to modify the shape of the radiation doses. HDR allows evaluation and subsequent fine-tuning of the implant in 3D before any treatment is given. Thus, a major advantage of HDR over LDR is that the dose to the prostate and to surrounding structures is known before any treatment is delivered. In addition, HDR allows for an improved ability to define and deliver the dose, by controlling the dwell times and positions of the iridium sources. This has important implications in that the high-dose area can be extended to cover extracapsular extension, whilst shaped to limit the dose to the urethra in an effort to reduce toxicity. In addition, permanent seeds have the potential for shifting within the prostate, and even migration to other structures over time, (bladder, rectum, urethra and lung) thereby increasing the uncertainty in dose distribution to the tumour [55]. This is not the case with HDR, where the sources are withdrawn back into the afterloader after treatment, and radiation exposure to both patient and staff are minimised. A further possible advantage is that the large dose fraction sizes associated with HDR monotherapy might achieve superior tumour control compared with LDR especially if prostate cancer possesses a high sensitivity to dose fractionation (i.e., if the α/β ratio is low [see later]) [56].

7.4. Selection criteria

The criteria for patient selection are important when considering use of brachytherapy as a sole modality of treatment. They are based not only on identifying those that have organ-confined disease, and at low risk of developing metastatic disease (PSA < 10 ng/ml, stage up to T2a and Gleason Score <7) [57,58], but also predicting those who are likely to have a good functional outcome. The latter is based on prostate volume and urinary outflow symptoms at presentation. Studies have shown that those with a prostate volume of less than 35 cm^3 identified with transrectal ultrasound have a relatively low incidence of acute urinary retention and urinary morbidity [59]. In those with prostate volumes greater than 50 cm^3, a higher incidence of pubic arch interference is observed which can cause difficulties in implanting the lateral portion of the gland. Urinary flow symptoms can be objectively assessed by using the International Prostate Symptom (IPS) Score prior to treatment. Those with minimal urinary symptoms (i.e., score 0–8) have a low risk of acute retention and prolonged urethritis [60].

7.5. Toxicity profile

Side-effects are predominantly urinary, though bowel toxicity and erectile impotence are also known risks. Whilst there are potential complications of the procedure itself including perineal bleeding/haematoma and mild haematuria, these symptoms are usually mild and self-limiting. The acute urinary morbidity rate is higher than that for EBRT. Symptoms tend to be most prevalent up to two months after the implant and gradually settle down by 9 months. The risk of urinary retention is related to the pre-treatment IPS Score and is in the order of 10–15% [61].

In terms of late toxicity, the morbidity rate is not dissimilar to that of EBRT. Studies have shown a 1% chance of developing urinary incontinence [60]. The risk of developing urinary incontinence increases significantly when transurethral resection is performed, either before or after the procedure (5–6%) [62]. There is also the risk of developing a urethral stricture for which studies quote a figure of between 5% and 10% [63,64]. The risk of late rectal toxicity is dose- and volume-dependent. Figures quoted for grade 2 early toxicity are in the order of 10% at approximately 3 years [65]. High-dose rate monotherapy may reduce urinary and rectal toxicity as well as potency compared with permanent seed implantation [54].

The effect of brachytherapy on erectile dysfunction remains uncertain, though the risk of impotence is not as low as originally hoped. In one study, 100 men were analysed with a minimum follow-up of 12 months. All had localised prostate cancer and no previous prostate cancer surgery. The International Index of Erectile Function (IIEF) questionnaire was completed prior to treatment and at 3 monthly intervals post-implantation. 48% were potent prior to treatment and erectile function was maintained in 80% [66]. Pharmacological intervention, e.g., Viagra can improve the quality of erections in most patients and approximately 20% produce erections sufficient for vaginal penetration [67].

7.6. Clinical outcomes

In the absence of prospective randomised trials comparing brachytherapy with surgery or EBRT, it is difficult to make direct comparisons between the different modalities. This is largely due to patient selection, and the differences in clinical and surgical staging. However, there have been many single institution retrospective reports showing comparable efficacy in terms of cancer control rates as measured by PSA at 5 years. Less information is available for greater than ten years, although Ragde and colleagues report a 70% 10-year disease-free survival for 229 patients treated with brachytherapy +/− EBRT, of which 147 received brachytherapy alone [68]. These figures are comparable to surgery or EBRT.

Although brachytherapy used in combination with EBRT, may increase 5-year tumour control rates compared with monotherapy, it is substantially more expensive and is likely to be at the expense of increased

morbidity [69]. It is also important to bear in mind that brachytherapy requires considerable expertise and is technically demanding with few centres having the necessary facilities for its implementation. There is also uncertainty about the benefit of additional hormones following high-dose radiation, as this may cause undue toxicity with little therapeutic gain [70].

8. New developments

8.1. Hypofractionation-exploiting the low alpha/beta ratio

Recent developments in understanding of the radiobiology of prostate cancer may have important implications for dose-fractionation of radiotherapy. Modelling exercises based on comparisons of the efficacy of conventionally fractionated radiotherapy with that of brachytherapy have suggested that the alpha/beta ratio (a measure of fractionation sensitivity) is between 0.8 and 3 Gy rather than the higher value of 8–10 Gy associated with most cancers [71]. If these estimates are accurate then using hypofractionated (>2 Gy/fraction) radiotherapy should increase tumour control and reduce late normal tissue toxicity.

Contemporary reports of hypofractionated schedules are limited. The Canadian PR5 trial randomised 936 patients with localised prostate cancer to receive either 66 Gy in 33 fractions or a hypofractionated regime of 52.5 Gy in 20 fractions. This trial suggested similar efficacy for the two groups in terms of overall survival, positive biopsy rates at 2 years and late toxicity [72]. The Christie Group have reported their experience using a fractionation schedule of 50 Gy in 16 fractions using conformal radiotherapy techniques in 705 men. Grade 2/3 rectal toxicity was 5% which is similar to published data for conventional fractionation schedules [73]. The Royal Marsden Hospital is leading a randomised trial to test the hypothesis that hypofractionated radiotherapy schedules for localised prostate cancer will improve the therapeutic ratio by either improving tumour control or reducing normal tissue side-effects. Schedules of 60 Gy in 20 and 57 Gy in 19 fractions are being compared with standard treatment of 74 Gy in 37 fractions.

8.2. Improving target localisation

Verification of the accuracy of radiotherapy delivery has depended on the visualisation of bony landmarks on portal imaging at the time of treatment, and comparison with reference images obtained during treatment planning. However, it is known that the prostate moves with respect to bony landmarks, particularly due to rectal filling. A range of techniques have been developed to improve the accuracy of daily prostate localisation. An example is the use of a commercial ultrasound based system -BAT (developed by the Nomos Corporation) that can be used to correct for inter-fractional prostate movement [74,75]. This involves the acquisition of transverse and sagittal suprapubic ultrasound images, upon which the patient's initial CT scan can be co-registered and overlaid. The necessary couch shifts are then calculated so that alignment between the CT scan and ultrasound occurs. Although ultrasound allows for a quick, non-invasive method of localising the prostate, and initial experience from small studies give cause for optimism, more recent reports highlight some inaccuracies and systematic errors that warrant further investigation. The observed errors may be in part due to the pressure exerted by the ultrasound probe causing movement of the prostate, [75,76] and the inter-user variability observed may be inherent to the process of aligning structures obtained from different imaging modalities [75].

The position of the prostate itself rather than bony anatomy can be determined at the time of treatment by the use of implanted intra-prostatic fiducial markers visualised on portal imaging. Studies show that this provides a feasible and precise technique of visualising the prostate during irradiation and correcting for its position [77]. Most studies have not shown significant seed migration [78]. To date, these methods have largely been used to detect and correct for inter-fraction prostate movement. However, the prostate gland moves not just between treatments, but also during treatment. The next step which is in development is to use an optical camera system to track the position of the fiducial markers by CT or 3D Ultrasound. Such a device may allow for the linear accelerator to be triggered only when the fiducial markers are in alignment – real-time tumour-tracking radiotherapy [79].

8.3. Improving target definition

Radiotherapy planning techniques are being developed to use magnetic resonance imaging (MRI), rather than CT, to define the prostate gland [80]. Using MRI as the 'gold standard' to define the prostate, CT has been shown to significantly overestimate the volume of the gland [81]. Thus, target localisation using MRI rather than CT will reduce the size of the clinical target volume (CTV) and hence the risk of toxicity. The development of cine-MRI has been used to study interfractional prostate and rectal movements [82].

9. Conclusions

Significant technical advances in recent years have permitted the development of safe, high-dose radiotherapy techniques for localised prostate cancer. 3D-CRT and IMRT have allowed dose escalation, and although this has yet to demonstrate an impact on overall

survival, the effects on biochemical control are encouraging. The combination of androgen deprivation with conventional dose radiotherapy has also produced noteworthy improvements in outcome. The group of patients who will benefit most from dose escalation has not been identified definitively. In low-risk patients, for whom conventional doses are adequate, dose escalation may just increase the risk of toxicity with no benefit in terms of disease control. The question of whether androgen deprivation will preclude the need for dose escalation, or whether androgen deprivation may be unnecessary when higher dose levels are administered remain unanswered.

Areas under active research include improving imaging techniques for target volume definition, dose individualisation and developing methods for verifying precise geometric and dosimetric accuracy of treatment delivery. These techniques will go a step further to achieving that traditional basic radiotherapy paradigm of improving the therapeutic ratio-maximising tumour cure while reducing normal tissue toxicity.

Conflict of interest statement

None declared.

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