Radiotherapy and combined modality approaches in localised prostate cancer

David P. Dearnaley

The Institute of Cancer Research and The Royal Marsden NHS Trust, Academic Unit of Radiotherapy, Sutton, Surrey, UK

Introduction

Controversy will continue to surround the optimal individual management of localised prostate cancer until we have more accurate tools to predict both the local behaviour and metastatic potential of the disease. At present, it seems reasonable to offer curative treatment to men judged to have a life expectancy of 10 years or more, although this may be modified to 5 years for men who have poorly-differentiated cancers [1,2]. The relative merits of radical radiotherapy or surgery depend both on the local tumour control probability and treatment induced morbidity. No adequate studies have compared these treatment alternatives and both should be considered as standard management options for patients with disease confined to the prostate [3,4]. The comparisons that have been made between the two options suggest that there is little difference in outcome [5]. It can be argued that success or failure of treatment is more dependent on tumour biology than treatment method, and treatment-related morbidity on the skill of the individual specialist rather than the treatment modality employed. There has been considerable development of radiotherapy techniques and strategies over the last ten years. Conformal radiotherapy has now become the standard of care as a result of prospective phase III randomised trials. Initial (neoadjuvant) hormone therapy is widely employed and has been shown to improve both local and biochemical control of disease. Studies of adjuvant hormonal treatment and radiotherapy have additionally shown that there is a survival advantage for longer term androgen suppression for men with more advanced poorly-differentiated cancers. Sophisticated radiotherapy techniques now allow high doses of radiation to be given and preliminary results strongly suggest improved control rates with very acceptable levels of long-term morbidity.

Selection of patients for radical radiotherapy

Radical radiotherapy should be reserved for those patients presenting without evidence of distant metastasis. The prognosis of patients with incidental (T1a) focal well-differentiated disease is so good [6] that immediate treatment is difficult to justify. Patients with T1b, T1c and T2–T3 disease are suitable for radical treatment depending on their age and general state of health. The decision to offer treatment is based on a judgement of the balance between the life expectancy of an individual patient and a chance of their disease progressing during this period of time [7]. The probability of curative treatment is high for small volume relatively well-differentiated cancers. As tumour bulk increases so does the chance of seminal vesicle or lymph node involvement and patients with lymph node involvement have a 75% chance of developing metastatic disease within 5 years [8]. If lymph node involvement is shown then radical local treatment (with surgery or radiotherapy) is inappropriate when used alone, although there is some evidence that combination with long-term androgen suppression may give improved results (see below). The prostate-specific antigen (PSA) level at presentation also gives a valuable guide to likely treatment outcome [9,10]. Currently, tumour stage, histological grade (usually Gleason score) and presenting PSA levels are very commonly used to stratify patients to receive neoadjuvant or adjuvant hormonal therapy in addition to modifying radiation dosage.

Results of radical external beam radiotherapy alone

Following external beam radiotherapy long-term clinically assessed local tumour control is good for patients with stage T1 cancers (83% at 15 years), but becomes less secure with increasing T-stage, falling to 65–68% for T2 and 44–75% for T3 cancers (Ta-

Table 1
External beam radiotherapy for cancer of the prostate: long-term results from Patterns of Care Surveys, Radiotherapy and Oncology Group studies and large single institute series

		Local recurrence (%)			Survival with no evidence of disease (%)			Overall survival (%)		
	Number	5 year	10 year	15 year	5 year	10 year	15 year	5 year	10 year	15 year
T1NX	583	3–6	4–8	17	84–85	52–68	39	83–95	52–76	41–46
T2NX	1117	12–14	17–29	32–35	66–90	27–85	15–42	74–78	43–70	22–36
T3NX	2292	12–26	19–31	25–56	32–60	14–46	17–40	56–72	32–42	23–27

References: Pilepich et al. [12], Goffinet and Baghaw [73], Zagars et al. [27], Perez et al. [74].

ble 1). There is general agreement that a positive biopsy 24 months post-radiotherapy indicates persisting disease [11]. Reported incidence of positive biopsy vary from 18 to 45% post-treatment and increases with disease bulk from 15% for men with B1 disease (<1.5 cm nodule) to 68–79% for men with bulky stage B or C cancers [12,13].

It has become clear that PSA estimation both before and after irradiation can give very useful prognostic information to guide the selection of patients for treatment, as well as being a very sensitive indicator of disease recurrence. Hanks et al. [14] studied 110 patients with T1–3 prostate cancer with a mean follow-up of 12.6 years and found long-term biochemical control in 72% of T1 cancers, 54% of T2A cancers, falling to 22% and 28% for bulky T2 and T3 cancers, respectively. Favourable outcome was also seen in cancers of low Gleason score which had a 75% rate of biochemical control compared to only 18% for Gleason 7 and 0% of Gleason 8 or 9 carcinomas. We have also learnt that pretreatment PSA levels are of critical importance [9,10,15–17]. For example, Hanks et al. found that for 120 patients with PSA more than 20 ng/ml at presentation only 28% remained biochemically free of progressive disease at 4 years, although 81% still had no evidence of distant metastasis, which suggests that locoregional recurrence may be a major component of disease failure.

A recent multi-institutional pooled analysis [9] has reported on a total of 1765 men with stage T1b, T1c and T2 tumours. They found that presenting PSA level was a powerful predictor of outcome, and the estimated rates of remaining free of biochemical (PSA) recurrence, according to pretreatment PSA values, were 81%, 68%, 51% and 31% for men presenting with pretreatment PSA values of less than 10 ng/ml, 10–19 ng/ml, 20–29 ng/ml, and at least 30 ng/ml, respectively. These results are currently a bench mark against which other treatment approaches should be measured. Another important conclusion from this study was that biochemical or clinical recurrence was unlikely more than 5 years after treatment (95% of patients remained free from failure if PSA levels were controlled at 5 years) and this result has been substantiated by other authors [18,19].

Complications after conventional external beam radiotherapy

Radiation-induced complications are dose-limiting, and conventional radiotherapy doses and fractionation schedules have been derived from years of clinical experience to give acceptable morbidity. Acute side-effects from radiotherapy to the pelvis include acute proctitis causing rectal discomfort and diarrhoea, acute cystitis producing dysuria and urinary frequency, and occasional skin reactions. Reported incidence range between 70–90% for mild symptoms, 20–45% for moderate, and 1–4% for severe or prolonged reactions [20–22]. Such side-effects depend on the volume of tissue irradiated (eg. pelvis and prostate or prostate only) [23] and also relate to the treatment technique. Acute side-effects are expected to settle within 4–6 weeks of completing radiotherapy.

Late complications may develop months to years after treatment and are potentially of more concern. Late gastrointestinal side-effects include persistent rectal discharge, tenesmus and rectal urgency, rectal bleeding, ulcer or stricture. Important late genitourinary complications include chronic cystitis, bladder ulcer, urinary incontinence, urethral stricture and impotence.

Results from over 1000 patients treated in a single-institute series suggest an overall moderate complication rate of 16–19%, with severe complications requiring surgical correction in 1–3% of cases [24–26]. Poor treatment technique and doses above 70 Gy were also associated with increase complications [27]. With a 10-year follow-up, 2% of patients had needed surgical correction of complications, and a further 2% had developed a major complication not requiring surgery, and two patients had died from

treatment-related side-effects. The actuarial 5- and 10-year complication-free survival rates were 93% and 86%, respectively [28]. An increase in the overall complication rate from 6 to 11% was noted for patients treated to doses below and above 65 Gy, respectively [29]. Impotence has been estimated to occur in between 30–40% of treated men, usually during the six months after treatment [30]. In a recent Radiation Therapy Oncology Group (RTOG) randomised study [31], 76% of men who were sexually potent before treatment reported return of sexual function. In a report of conformal therapy [32], 62% of men reported return of sexual function. However, patients have consistently reported a higher level of morbidity than may be appreciated from scales of physician-based reporting [33]. For men between the ages of 55 and 59 years, 75% were bothered by sexual dysfunction after surgery compared to 40% after radiotherapy; for those men aged between 60–74 years, the figures were 53% and 47%, respectively, 2 years after treatment. Global measures of quality of life appear virtually unaffected by treatment [32–36].

Approaches to improve the results of radiotherapy

Although radical radiotherapy is successful in obtaining clinically judged local control of disease in the majority of patients with T1 to T3 disease, the development of metastatic disease is a major problem, particularly for more bulky disease presentations and for those cancers with high presenting PSA levels or poorly-differentiated pathology. Different, but complementary approaches are being developed to improve results using radiotherapy (Table 2). These are either methods to (a) improve the local control of disease; increasing radiation dose in a variety of ways or employing the initial use of neoadjuvant hormone therapy or (b) the use of systemic adjuvant androgen blockade (an analogy can be made with the use of tamoxifen in breast cancer) to reduce the risk of development of metastasis.

Conformal radiotherapy

As previously described, the complication rate from standard prostate radiotherapy increases with increasing dose so that doses above 65–70 Gy are associated with unacceptable complications. The principle dose-limiting late complication is proctitis due to radiation of the rectum. Nevertheless, retrospective data have shown improvement in local control using higher doses of radiation. For example, the Patterns of Care Studies Group [37] reported results from 1348 men with stage B and C cancers. The actuarial 5-year local recurrence rate for stage C disease was 37% for doses less than 60 Gy, 36% for 60–64 Gy, 28% for 65–69 Gy and 19% for doses of more than 70 Gy. Dose escalation therefore seems justified.

Conformal radiotherapy is a new technology developed over the last 10 years or more to enable radiation fields to be shaped accurately to follow the outline of the target tissues. The process involves, firstly, the 3-dimensional (3D) visualisation of target structures (in this case prostate with or without seminal vesicles). This is achieved using closely collimated computed tomography (CT) slices which are then reconstructed in 3 dimensions so that shaped rather than the conventional rectangular radiation beams can encompass the target. There have been considerable developments in radiotherapy outlining and planning software so that these procedures can be now undertaken rapidly and routinely. The radiation beams are most conveniently shaped with a multileaf collimator which are now routinely installed on the majority of new linear accelerators. Verification of accuracy is a very important part of the process and this can now be insured by taking electronic portal images of the radiotherapy treatment fields which can be directly compared with simulator films or, ideally, digitally reconstructed radiographs from the original CT images. Using these methods, the amount of excess normal tissue treated is reduced by approximately 50%. Conformal and conventional radiotherapy for prostate cancer have been formally compared in a prospective phase III trial using a

Table 2
Methods to improve results of radical radiotherapy for prostate cancer

	Improve local control	Reduce risk of development of metastases
Increase dose	• Conformal radiotherapy • Intensity modulated radiotherapy • Brachytherapy • Particle beam therapy	Systemic treatment: androgen blockade
Neoadjuvant hormonal therapy		Reduce local treatment failure

standard radiation dose of 64 Gy [38]. Men were randomly allocated conformal or conventional radiotherapy treatments. Significantly fewer developed radiation-induced proctitis and bleeding in the conformal group than the conventional group (37% vs 56% $\geq$ RTOG grade 1, $P = 0.004$; 5% vs 15% $\geq$ RTOG grade 2, $P = 0.01$). After a median follow-up of 3.6 years, there was no difference between the groups in local tumour control. This study has laid a firm scientific foundation for the introduction of conformal radiotherapy in routine practice and also for escalating dose using conformal radiotherapy techniques.

Dose-escalation studies using 3D-conformal radiotherapy have been reported by several North American groups [15,16,39]. Zelefesky et al. [15] reported that complete response (defined as PSA = 1.0 ng/ml) occurred in 90% of patients receiving 75.6 Gy or 81 Gy compared to 76% and 56% for those treated to 70.2 Gy and 64.8 Gy respectively ($P < 0.001$). Five year actuarial PSA relapse-free survival was significantly improved in patients with intermediate or unfavourable prognosis receiving 75.6 Gy or more ($p < 0.05$). The positive biopsy rate at 2.5 years or longer after 3D-conformal radiotherapy was 7% in patients receiving 81 Gy, 48% after 75.6 Gy, 45% after 70.2 Gy, and 57% after 64.8 Gy ($P < 0.05$), although the number of patients was small. Additionally, Hanks et al. [16] have reported that in patients with initial PSA $\geq$ 10 ng/ml, 2 year PSA control rates were 85% for patients who received more than 71 Gy compared with 72% for those who received lower doses ($P = 0.007$). Similarly, a recent multi-institutional review [40] demonstrated improved biochemical control 5 years after completion of treatment for high grade T1 and 2 cancers treated to a dose above 70 Gy. The first report of an overall improvement in survival has come from the North American RTOG [41]. Pooled data from 1465 men treated in RTOG studies showed that for men with high grade cancers a higher radiation dose ($\geq$66 Gy versus $\leq$66 Gy) was associated with a 29% lower risk of death from prostate cancer and a 27% reduction in the overall mortality rate ($P < 0.05$). A substantial body of data from randomised control trials of dose escalation will become available within the next few years. The first trial to report was performed by the MD Anderson Cancer Centre. They randomised a total of 305 men to receive either 70 Gy delivered using conventional radiotherapy techniques or 78 Gy using conformal radiotherapy methods. The failure-free survival rates at 5 years were 69% and 79%, respectively, ($P = 0.06$) with multivariate analysis showing a significant benefit for men with a presenting PSA level of >10 ng/ml [42].

In the UK, a large randomised trial will complete recruitment in 2001. Following a pilot study undertaken at the Institute of Cancer research and Royal Marsden Hospital, a total of over 900 men will be randomised to receive either 64 Gy or 74 Gy using conformal radiotherapy methods following initial androgen suppression for 3–6 months [43]. A complementary study undertaken by the National Cancer Institute in Amsterdam will randomise approximately 600 men to receive either 70 or 78 Gy again using conformal radiotherapy techniques in both arms of the study. Meta-analysis of these and additional trials will in due course adequately define the role of dose escalation in different subgroups of patients, assessing overall and disease-specific survival benefits — as well as impact on PSA control and treatment-related side-effects. The importance of maintaining therapy-related morbidity to a minimum is essential. Already the Memorial Sloane Kettering group have shown that with very meticulous technique and scrupulous shielding of the rectum that it is possible to treat patients to between 75 and 81 Gy with a low rate of long-term rectal complications [44] and using very sophisticated intensity modulated radiotherapy techniques, this group have reported a two year actuarial risk of grade 2 bleeding and proctitis of only 2% [45].

It will be a challenge for the radiotherapy community to implement such methods routinely.

Combined modality treatment using androgen suppression and radiotherapy

Laboratory and both preliminary and phase III randomized clinical trials have now demonstrated clear advantages from using combinations of hormonal therapy with radiotherapy in the management of localised prostate cancer. Hormonal treatment can be given prior to radiation for a period of 2–6 months or more (neoadjuvant therapy) or alternatively may be used in an adjuvant fashion continuing after radiotherapy for periods of two years or more. Neoadjuvant hormonal therapy is complementary to attempts to improve results of radiotherapy using conformal radiotherapy with or without dose escalation (Fig. 1). However, we have not yet learnt what is the optimal combination of these different approaches. It is also at present unclear as to the precise definition of groups of patients which may benefit from adjuvant treatment, although both of these issues will be resolved as data from current phase III studies becomes available.

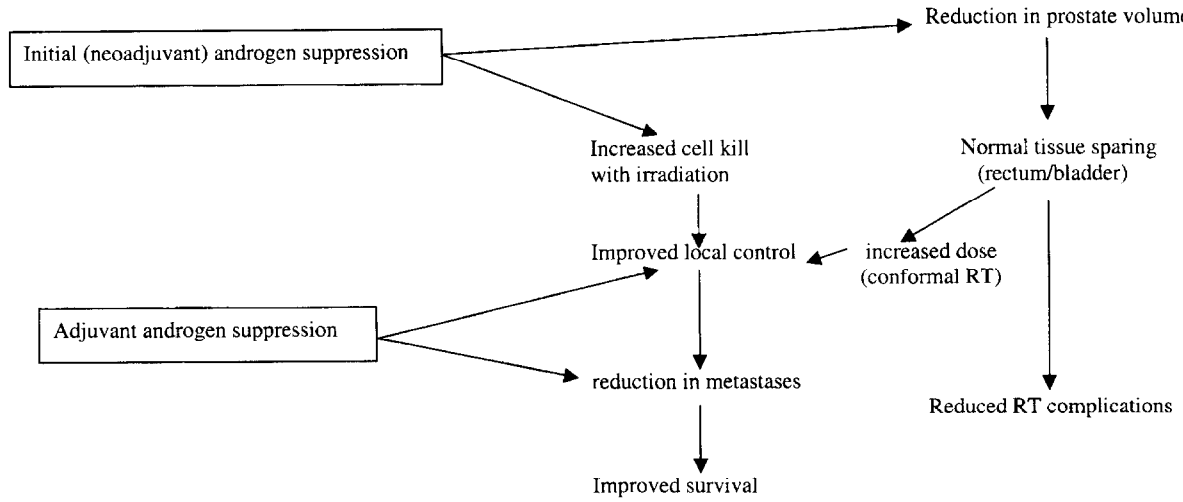

Fig. 1. Combined modality treatment using androgen suppression and radiotherapy.

Clinical studies of neoadjuvant androgen suppression and radiotherapy

Combined modality treatment using initial hormones followed by radiotherapy can potentially have advantages in two ways (Fig. 1). Firstly, the prostate and radiotherapy target volume may be decreased leading to a benefit in therapeutic ratio and, secondly, as in the experimental models [46,47], there may be an additive or supra-additive effect on prostate cancer cell death. Different groups of researchers have shown very similar results for reduction of radiotherapy volumes with 25–41%, 23–25% and 21–50% reduction in prostate target volume and volumes of rectum and bladder treated to high doses [48–50].

Phase III trials of initial hormonal treatment and radiotherapy

Three phase III trials have now reported the results of comparisons of radiotherapy with or without neoadjuvant androgen deprivation. The first and largest undertaken by the RTOG randomized 471 patients with large primary tumours (T2–T4) and no evidence of distant metastases to receive maximal androgen blockade using goserelin and flutamide 2 months before and during radiation treatment (group I) or radiation therapy alone (group II) [51]. The most recently reported results show highly significant benefits in 5 year rates of local disease control (group I 75%, group II 64%, $P = 0.002$), freedom from distance metastases (group I 71%, group II 61%, $P = 0.03$), and no evidence of disease including PSA failure (group I 39%, group II 20%, $P < 0.0001$). After 8 years of follow-up, there is a suggestion that the survival in group I (51%) may be improved compared to group II (42%), although this result does not reach statistical significance ($P = 0.2$) [52]. In a similar, but smaller, Canadian Urological Oncology Group study 208 patients with stage B2–C prostate cancer were randomly allocated to a 12-week initial course of cyproterone acetate followed by radiotherapy (group I) or radiotherapy alone (group II). On average, the PSA nadir was lower in the combined modality group and more patients in group I remained free of clinical (71% vs 49%, $P = 0.02$) or biochemical (47% vs 22%, $P = 0.001$) recurrence and, additionally, after 18 months, there was a significant improvement in the number of patients who had negative post-treatment prostate biopsies [53]. Additionally, in a small three-arm randomized study from Quebec [54], 120 patients were randomized to receive radiotherapy alone, radiotherapy with an initial 3-months course of maximum androgen blockade, or maximum androgen blockade for a total of 11 months. Two-year post-treatment biopsy results showed residual cancer in 65%, 28% and 5% of these three groups respectively. Taken together, these three clinical studies provide very strong evidence that initial androgen suppression improves the local control that can be achieved with radiation treatment and the finding that metastases are reduced indicates that the natural history of the disease is favourably modified. In consequence, initial hormone treatment has become the standard of care for appropriate sub-groups of men with localised prostate cancer (see below) and is being studied in combination with conformal radiotherapy techniques in the current Medical Research Council RT01 Trial [43]. The relative effects of combined modality treatment or high-dose radiotherapy require further study. It is also possible that

anti-androgen monotherapy with, for example, bicalutamide may in the future give a more acceptable side-effect profile.

Adjuvant androgen deprivation in combination with radiotherapy

The rationale for long-term adjuvant androgen ablation is to employ treatments which demonstrate 'spatial co-operation' in an attempt to effectively treat micrometastatic disease beyond the scope of a local treatment modality. This approach is now well accepted, for example, in the management of localised breast cancer where adjuvant hormone therapy produces a significant benefit for both recurrence and survival.

In prostate cancer, five randomized controlled trials have reported results. The largest of these was performed by the RTOG (Protocol 85-31) in which 977 men were randomized to receive either radiotherapy to the prostate and pelvis, or radiotherapy and androgen deprivation [55]. Hormonal treatment was given using a luteinising hormone-releasing analogue (LHRHa) which commenced during the last week of radiotherapy and continued indefinitely. The control group commenced goserelin at the time of relapse. Eligible patients had T3 disease or T1–T2 disease with lymph node involvement. Post-prostectomy patients with adverse features were also eligible. The trial has recently been updated with median follow-up of 6 years [56]. Eight-year actuarial results showed significant differences between the groups in local treatment failure (23% vs 37%, $P < 0.0001$), development of distance metastases (27% vs 37%, $P < 0.0001$) as well as biochemical control of disease. Overall survival was not statistically different between the two groups with 49% vs 47% survival at 8 years. However, subgroup analysis showed that patients with high grade (Gleason 8–10) cancers had a statistically significant improvement of both absolute ($P = 0.036$) and cause-specific survival ($P = 0.019$) if adjuvant hormonal therapy had been given. The EORTC have reported a similar study in which 415 men with either T3–T4 cancers or poorly-differentiated T1–T2 tumours were randomised between radiotherapy to the prostate and pelvis alone or to combined modality treatment with a LHRHa, which was commenced at the beginning of radiotherapy and continued for a period of 3 years [57]. Median follow-up at the time of reporting was 45 months. As in the RTOG study, results demonstrated an improvement in local disease control (77% vs 97%, $P < 0.001$), and patients surviving free of disease (48% vs 85%, $P < 0.001$), but also dramatic overall improvement in survival, with 52% of the radiation alone control group alive at 5 years compared to 79% of the combined modality group ($P = 0.001$). It is possible that the differences between the results of the RTOG and EORTC studies are due to patient selection, chance, or the timing of hormonal treatment both before and after radiotherapy.

In a small Swedish study (Table 3), 91 patients were randomized to receive either radiotherapy alone or combined modality treatment with orchiectomy preceding radiotherapy by approximately 6 weeks [58]. After a median follow-up of 9.3 years, clinical progression was seen in 61% of the radiotherapy only patients compared to 31% of the combined modality group ($P = 0.005$). Mortality in two groups was 61% and 38%, respectively, ($P = 0.02$) with cause-specific mortality of 44% and 27%, respectively, ($P = 0.06$). The Medical Research Council (MRC) have reported results of a three-arm study comparing radiotherapy, orchiectomy and combined modality treatment using radiotherapy and orchiectomy. A total of 277 patients were randomized and

Table 3
Trials of adjuvant hormonal treatment with radiotherapy

Trial identifier	No. of patients	Tumour stage		Randomisation and timing of hormonal treatment
RTOG 85-31	977	A2/B	D1	RT with LHRHa on relapse vs RT + LHRHa starting at end of RT given indefinitely
		C	D0/1	
EORTC 22863	415	T1–T2 T3–T4	G3	RT with LHRHa on relapse vs RT + LHRHa at start of radiotherapy
Sweden	91	T1–T4	No-3	RT vs orchidectomy (6 weeks pre–RT) and RT
MRC PRO2	277	T2–T4		RT vs orchidectomy and RT vs orchidectomy
RTOG 92-02	1554	T2c–T4		Initial androgen suppression + RT vs Initial androgen suppression + RT and adjuvant LHRHa for 2 years

RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; LHRHa = luteinising hormone-releasing analogue; MRC = Medical Research Council.

Table 4
Prognostic groups and impact of combined modality treatment in patients treated with radiotherapy for prostate cancer. Analysis of RTOG trials

Prognostic group	Description		Disease-specific survival (%)			Effects of combined modality treatment
			5 years	10 years	15 years	
I	T1–T2 Nx	GL2–6	96	86	72	Inadequate patient number to reach conclusion
II	(a) T3 Nx	GL2–6				Improvement of disease-specific survival at 8 years using neoadjuvant androgen suppression
	(b) T1–T2 Nx	GL7				
	(c) N +	GL2–6	94	75	61	
III	(a) T3 Nx • T1–T2 Nx • N +	GL7 GL8–10 GL7	83	62	39	20% improvement in overall survival at 8 years using long-term (adjuvant) androgen suppression
IV	(a) T3 Nx	GL8–10				
	(b) N +	GL 8–10	64	34	27	

GL = Gleason score.
RTOG = Radiation Therapy Oncology Group.

results [59,60] showed a significant lengthening of time for the development of metastases in the orchiectomy groups. Additionally, there was a gain in local control and survival with an approximately 10% improvement in overall survival in the orchiectomy and radiotherapy group compared to the group treated with radiotherapy alone. This difference failed to reach statistical significance. Unfortunately, in this trial radiotherapy was given in an unspecified manner compared to the strict quality control in other trials. Finally, the RTOG have performed a further study (Protocol 92-02) in which 1554 men have been treated with initial androgen suppression and radical radiotherapy and have then been randomized to either stop hormone treatment or continue for a period of 2 years. Preliminary analyses [61,62] have shown significant improvements (for the group that continued treatment) in local control (94% vs 84%, $P = 0.0001$), biochemical control of disease (79% vs 54%, $P = 0.0001$), and freedom from metastases (89% vs 83%, $P = 0.001$), but no overall improvement in disease-specific survival (92% vs 87%, $P = 0.07$). However, for patients with poorly-differentiated disease, there was a statistically significant improvement in both the disease-specific and overall survival rates.

In an attempt to identify groups of patients who may benefit from combined modality treatment, the RTOG group have under taken an overview of their radiotherapy studies [63] and identified four prognostic groupings. Trials that included a component of androgen suppression were then analysed [64]. Results appeared to show a survival benefit for risk group II patients, with bulky T2 or T3 disease treated with initial androgen suppression, and for group III and IV patients, who had a combination of T3, high grade and node-positive cancers, adjuvant hormonal therapy appeared to give a 20% higher survival at 8 years (Table 4). An insufficient proportion of group I patients had been treated with hormonal therapy to reach conclusions.

Conclusion

Future results from ongoing phase III trials will help to define optimal contributions of high dose conformal radiation or combined modality treatments with the aim of balancing the relative effectiveness and toxicities of different treatment approaches. Newer anti-androgens such as bicalutamide will need to be included in treatment strategies. For more advanced cancers, the additional value of radiotherapy to hormonal treatment alone is being tested in the NC1-Canada (Protocol PR3) led International Phase III trial (UK MRC PRO7).

Acknowledgements

This work was undertaken in The Royal Marsden national health service (NHS) Trust who received a proportion of its funding from the NHS Executive; the views expressed in this publication are those of the authors and not necessarily those of the NHS Executive. This work was supported by the Institute of Cancer Research, the Bob Champion Cancer Trust and the Cancer Research Campaign.This article is an abbreviated version of the text in "The clinical utility of external beam radiotherapy and hormone treatment for localised disease". To be published in Key Advances in the Effective Management of Prostatic Cancer. Aesculapius Medical Press.

References

1 Dearnaley DP, Melia J. Early prostate cancer — to treat or not to treat? Lancet 1997, 349(9056): 892–893.
2 Lu Yao GL, Yao SL. Population-based study of long-term survival in patients with clinically localised prostate cancer [see comments]. Lancet 1997, 349(9056): 906–910.
3 Consensus conference. The management of clinically localized prostate cancer. JAMA 1987, 20(258): 2727–2730.
4 COIN Guidelines. Guidelines on the Management of Prostate Cancer. Clin Oncol 1999, 11: S55–S88.
5 D'Amico AV, Whittington R, Kaplan I et al. Equivalent biochemical failure-free survival after external beam radiation therapy or radical prostatectomy in patients with a pretreatment prostate specific antigen of >4–20 ng/ml. Int J Radiat Oncol Biol Phys 1997, 37: 1053–1058.
6 Lowe BA, Listrom MB. Incidental carcinoma of the prostate: an analysis of the predictors of progression. J Urol 1988, 140: 1340–1344.
7 Chodak GW, Thisted RA, Gerber GS et al. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994, 330: 242–248.
8 Perez C, William R, Ihde D. Carcinoma of the prostate. In: VT DeVita, S Hellman, SA Rosenberg (Eds.), Cancer: Principle and Practice of Oncology. 3rd ed. Philadelphia, J.B. Lippincott Company, 1989, pp. 1023–1058 (vol. 1).
9 Shipley W, Thames H, Sandler H et al. Radiation therapy for clinically localized prostate cancer: A multi-institutional pooled analysis. JAMA 1999, 281: 1598–1604.
10 Kattan M, Zelefsky M, Kupelian P, Scardino P, Fuks Z, Leibel S. Pretreatment nomogram for predicting the outcome of three-dimensional conformal radiotherapy in prostate cancer. J Clin Oncol 2000, 18: 3352–3359.
11 Crook J, Robertson S, Collin G, Zaleski V, Esche B. Clinical relevance of trans-rectal ultrasound, biopsy and serum prostate-specific antigen following external beam radiotherapy for carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1993, 27: 31–37.
12 Scardino PT, Bretas F. Interstitial radiotherapy. In: Bruce AW, Trachtenberg J (Eds.), Adenocarcinoma of the Prostate. Springer-Verlag, London, 1987, pp. 145–158.
13 Freiha FS, Bagshaw MA. Carcinoma of the prostate: Results of post-irradiation biopsy. Prostate 1984, 5: 19–25.
14 Hanks GE, Hanlon AL, Hudes G, Lee WR, Suasin W, Schultheiss TE. Patterns-of-failure analysis of patients with high pretreatment prostate-specific antigen levels treated by radiation therapy: the need for improved systemic and locoregional treatment. J Clin Oncol 1996, 14: 1093–1097.
15 Zelefsky M, Leibel S, Gaudin P et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998, 41: 491–500.
16 Hanks GE, Hanlon AL, Schultheiss TE. Dose escalation with 3D conformal treatment: five year outcomes, treatment optimisation, and future directions. Int J Radiat Oncol Biol Phys 1998, 41: 501–510.
17 Hanks GE, Lee WR, Hanlon AL et al. Conformal technique dose escalation for prostate cancer: biochemical evidence of improved cancer control with higher doses in patients with pretreatment prostate-specific antigen > or = 10 ng/ml [see comments]. Int J Radiat Oncol Biol Phys 1996, 35: 861–868.
18 Vicini F, Kestin L, Martinez A. The correlation of serial prostate specific antigen measurements with clinical outcome after external beam radiation therapy of patients for prostate carcinoma. Cancer 2000, 88: 2305–2318.
19 Hanlon A, Hanks G. Failure pattern implications following external beam irradiation of prostate cancer: long-term follow-up and indications of cure. Cancer J Sci Am 2000 (Suppl 2): S193–197.
20 Duncan W, Warde P, Catton CN. Carcinoma of the prostate: results of radical radiotherapy (1970–1985). Int J Radiat Oncol Biol Phys 1993, 26: 203–210.
21 Amdur RJ, Parsons JT, Fitzgerald LT, Million RR. Adenocarcinoma of the prostate treated with external-beam radiation therapy: 5-year minimum follow-up. Radiother Oncol 1990, 18: 235–246.
22 Mithal N, Hoskin P. External beam radiotherapy for carcinoma of the prostate: A retrospective study. Clin Oncology 1990, 18: 297–301.
23 Sagerman RH, Chun HC, King GA, Chung CT, Dalal PS. External beam radiotherapy for carcinoma of the prostate. Cancer 1989, 63: 2468–2474.
24 Zagars GK, von Eschenback AC, Johnson DE, Oswald MJ. Stage C adenocarcinoma of the prostate: An analysis of 551 patients treated with external beam radiation. Cancer 1987, 60: 1489–1499.
25 Aristizabal SA, Steinbronn D, Heusinkveld RS. External beam radiotherapy in cancer of the prostate. Radiother Oncol 1984, 1: 309–315.
26 Forman JD, Zinreich E, Lee Ding-Jen, Wharam MD, Baumgardner RA, Order SE. Improving the therapeutic ratio of external beam irradiation for carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1985, 11: 2073–2080.
27 Leibel SA, Hanks GE, Kramer S. Patterns of care outcome studies: Results of the national practice in adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys 1984, 10: 401–409.
28 Hanks GE, Diamond JJ, Krall JM, Martz KL, Kramer S. A ten year follow-up of 682 patients treated for prostate cancer with radiation therapy in the United States. Int J Radiat Oncol Biol Phys 1987, 13: 499–505.
29 Hanks GE, Krail JM, Martz KL, Diamond JJ, Kramer S. The outcome of treatment of 313 patients with T-1 (UICC) prostate cancer treated with external beam irradiation. Int J Radiat Oncol Biol Phys 1988, 14: 243–248.
30 De Wit L, Ang KK, van der Schueren E. Acute side effects and late complications after radiotherapy of localized carcinoma of the prostate. Cancer Treat Rev 1983, 10: 79–89.
31 Pilepich MV, Krall JM, al Sarraf M et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. Urology 1995, 45: 616–623.
32 Roach MI, Chinn DM, Holland J, Clarke M. A pilot survey of sexual function and quality of life following 3D conformal radiotherapy for clinically localised prostate cancer. Int J Radiat Oncol Biol Phys 1996, 35: 869–874.
33 Potosky A, Legler J, Albertsen P et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. J Natl Cancer Inst 2000, 92: 1582–1592.
34 Litwin M, Hays R, Fink A et al. Quality-of-life outcomes in men treated for localized prostate cancer. JAMA 1995, 273: 129–135.
35 Beard CJ, Propert KJ, Rieker PP et al. Complications after treatment with external-beam irradiation in early-stage prostate cancer patients: a prospective multiinstitutional outcomes study. J Clin Oncol 1997, 15: 223–229.
36 Widmark A, Fransson P, Tavelin B. Self-assessment questionnaire for evaluating urinary and intestinal late side effects

after pelvic radiotherapy in patients with prostate cancer compared with an age-matched control population. Cancer 1994, 74: 2520–2532.

37 Hanks GE, Martz KL, Diamond JJ. The effect of dose on local control of prostate cancer. Int J Radiat Oncol Biol Phys 1988, 15: 1299–1305.

38 Dearnaley DP, Khoo VS, Norman A et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 1999, 353: 267–272.

39 Sandler HM, Perez-Tamayo C, Ten Haken RK, Lichter AS. Dose escalation for stage C(T3) prostate cancer: minimal rectal toxicity observed using conformal therapy. Radiother Oncol 1992, 23: 53–54.

40 Fiveash J, Hanks GMR et al. 3D conformal radiation therapy (3DCRT) for the high grade prostate cancer: a multi-institutional review. Int J Radiat Oncol Biol Phys 2000, 47: 335–342.

41 Valicenti R, Lu J, Pilepich M, Asbell S, Grignon D. Survival advantage from higher-dose radiation therapy for clinically localized prostate cancer treated on the Radiation Therapy Oncology Group Trials. J Clin Oncol 2000, 18: 2740–2746.

42 Pollack A, Zaggars G, Smith L et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 2000, 18: 3904–3911.

43 Seddon B, Bidmead M, Wilson J, Khoo V, Dearnaley D. Target volume definition in conformal radiotherapy for prostate cancer: quality assurance in the MRC RT-O1 trial. Radiother Oncol 2000, 56: 73–83.

44 Zelefsky M, Cowen D, Fuks Z et al. Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localised prostate carcinoma. Cancer 1999, 85: 2460–2468.

45 Zelefsky M, Fuks Z, Happersett L et al. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol 2000, 55: 241–249.

46 Zietman AL, Prince EA, Nakfoor BM, Park JJ. Androgen deprivation and radiation therapy: sequencing studies using the Shionogi in vivo tumour system. Int J Radiat Oncol Biol Phys 1997, 38: 1067–1070.

47 Joon DL, Hasegawa M, Sikes C et al. Supra-additive apoptotic response of R3327-G rat prostate tumours to androgen ablation and radiation. Int J Radiat Oncol Biol Phys 1997, 38: 1071–1077.

48 Dearnaley D. Combined modality treatment with radiotherapy and hormonal treatment in localised prostate cancer. In: A Belldegrun, RS Kirby, DWW Newling (Eds.), New Perspective in Prostate Cancer, 2nd ed. Isis Medical Media, 2000, pp. 169–180.

49 Forman JD, Kumar R, Haas G, Montie J, Porter AT, Mesina CF. Neoadjuvant hormonal downsizing of localised carcinoma of the prostate: effects on the volume of normal tissue irradiation. Cancer Invest 1995, 13: 8–15.

50 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.

51 Pilepich MV, Sause WT, Shipley WU et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomised comparative trial of the radiation therapy Oncology Group. Urology 1995, 45: 616–623.

52 Pilepich MV, Winter K, Roach M et al. Phase III Radiat Oncol Group (RTOG) 86-10 of androgen deprivation before and during radiotherapy in locally advanced carcinoma of the prostate. Proc Am Soc Clin Oncol 1998, 17(Abstract 1185): 308a.

53 Porter A, Ethliali M, Manji Mea. A phase III randomised trial to evalute the efficacy of neoadjuvant therapy prior to curative radiotherapy in locally advanced prostate cancer patients. A Canadian Urologic Oncology Group study. Proc Am Soc Clin Oncol 1998, 17: 315a (Abstract 1123).

54 Laverdiere J, Gomez JL, Cusan L et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. Int J Radiat Oncol Biol Phys 1997, 37(2): 247–252.

55 Pilepich MV, Caplan R, Byhardt RW et al. Phase III trial of androgen suppression using goserelin in unfavorable-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.

56 Lawton C, 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 unfavorable prognosis carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001, 49: 937–946.

57 Bolla M, Gonzalez D, Warde P et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin [see comments]. N Engl J Med 1997, 337(5): 295–300.

58 Granfors T, Modig H, Damber JE, Tomic R. Combined orchiectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: a prospective randomized study. J Urol 1998, 159: 2030–2034.

59 Fellows GJ, Clark PB, Beynon LL et al. Treatment of advanced localised prostatic cancer by orchiectomy, radiotherapy, or combined treatment. A Medical Research Council Study. Br J Urol 1992, 70: 304–309.

60 Dearnaley DP, Horwich A, Shearer RJ. Treatment of advanced localised prostatic cancer by orchidectomy, radiotherapy or combined treatment. A Medical Research Council Study. Br J Urol 1992, 72: 673–674.

61 Hanks G, Lu J, Machtay M et al. RTOG Protocol 92-02: A Phase III Trial of the Use of Long Term Androgen Suppression Following Neoadjuvant Cytoreduction and Radiotherapy in Locally Advanced Carcinoma of the Prostate. Proc Am Soc Clin Oncol 3 2000, 327a (Abstract 1284).

62 Horwitz E, Winter K, Hanks G, Lawton C, Russell A, Machtay M. Subset analysis of RTOG 85-31 and 86-10 indicates an advantage for long-term vs. short-term adjuvant hormones for patients with locally advanced nonmetastatic prostate cancer treated with radiation therapy. Int J Radiat Oncol Biol Phys 2001, 49: 947–956.

63 Roach III M, Lu J, Pilepich M et al. Four prognostic groups predict long-term survival from prostate cancer following radiotherapy alone on radiation therapy oncology group clinical trials. Int J Radiat Oncol Biol Phys 2000, 47: 609–615.

64 Roach III M, Lu J, Pilepich M 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.