Radiotherapy in locally advanced prostate cancer

David P. Dearnaley

Academic Radiotherapy, Institute of Cancer Research/Royal Marsden Hospital, Sutton, United Kingdom

Introduction

External Beam Radiotherapy has been commonly employed for the management of advanced localised prostate cancer. Recent developments in conformal radiotherapy (CFRT) and now intensity modulated radiotherapy (IMRT) permit the safe introduction of high dose treatments and phase III trials have given an improved understanding of the benefit and role of both short and long course hormonal therapy. While these studies have given good evidence that androgen suppression improves outcome when added to radiotherapy, controversy remains concerning the appropriate dose, fractionation and radiotherapy treatment volumes. Additionally, many men presenting with locally advanced disease will be well palliated with hormone therapy alone. Valuable guidance concerning the additional role of radiotherapy will come from the current collaborative trial between the National Cancer Institute of Canada (NCIC) (PR3) and UK Medical Research Council (MRC) (PR07) which is addressing this issue by randomising men with locally advanced disease to either hormonal therapy alone or to combined modality treatment. This article will review evidence relating to these different aspects of management strategy highlighting recent results to inform current practice.

Definition of locally advanced disease

Localised prostate cancer can be divided into low, intermediate and high risk prognostic groups. There are two commonly used systems which show considerable overlap. The Memorial Sloan Kettering group [1,2] define low risk as T1 or T2 disease, Gleason score of 6 or less and an initial PSA of $\leqslant$10 ng/ml. Intermediate risk patients have one of the prognostic indicators with a higher value and unfavourable prognosis is given for men with two or more indicators with higher values. D' Amico [3] has defined low risk as Stage T1c/T2a and PSA level $\leqslant$10 ng/ml and Gleason score $\leqslant$6; intermediate risk as T2b or Gleason 7 or PSA level 10 – $\leqslant$20 ng/ml; high risk as T2c or PSA > 20 ng/ml or Gleason score $\geqslant$8. Locally advanced disease may include some patients in the intermediate and unfavourable groups as well as patients with T3 or greater disease or evidence of pelvic lymph node involvement. Patients with various combinations of poor risk features have been included in studies of patients with "advanced" localised prostate cancer and interpretation of results in any particular patient sub-group needs to be considered with care.

Patient and tumour assessment

All patients should have appropriate clinical examination including digital rectal examination, histopathology assessment using the Gleason scoring system and serum Prostate Specific Antigen (PSA) measurement in addition to routine haematological and biochemical parameters. The purpose of additional imaging is to more precisely define likely patterns of disease spread in an individual patient so as to customise treatment. There have been considerable advances and continuing new developments in imaging techniques. Currently, Magnetic Resonance Imaging (MRI) is the preferred method of pelvic assessment recommended by The Royal College of Radiologists in the UK [4]. Imaging is unlikely to detect abnormalities in men with lower presenting PSA levels and Gleason Grades [5] but more recent studies are showing increased sensitivity and specificity for MRI particularly if images are read by specialist radiologists [6]. Prostate cancer staging using MRI is more closely related to survival outcome than clinical staging [7]. In the future, MR spectroscopy and dynamic contrast enhanced MRI may increase precision further [8,9]. Risk of lymph node involvement may be estimated from clinical stage, Gleason grade and presenting PSA level [10]. Computed Tomography (CT) and conventional MRI can detect enlarged lymph nodes (upper limit of normal 10 mm [11]) but for patients with a high risk of lymph node involvement; currently surgical lymph node sampling remains the definitive diagnostic

technique and the laparascopic approach, in expert hands, can reduce morbidity [12]. However, full sampling of the lymph node areas at risk is not possible [13,14] and in the future more accurate, non-invasive lymph node assessment using MRI with ultra-small para-magnetic iron oxide contrast agents [15,16] may prove the evaluation of choice.

Technetium bone scans are the standard method for detecting skeletal involvement and are recommended for patients with intermediate risk disease or more [17]. Our own practice is now to perform MRI looking for spinal bone marrow metastases [18] in men presenting with very unfavourable characteristics such as high grade pathology *and* high presenting PSA levels (e.g. over 30 ng/ml) or pelvic lymph node involvement. Such evaluation would be limited to men in whom high dose radiotherapy techniques were being considered in addition to long term androgen suppression and is not yet routinely available.

Results of conventional dose radiotherapy alone

The long term outcome of patients with T1–T3 prostate cancer treated with external beam therapy alone during the 1970s and 80s in the pre-PSA era has been documented by the USA Patterns of Care (POC) Study Group, Radiation Therapy Oncology Group (RTOG) randomised studies and other large single institutional series [19–24]. The POC and RTOG study group results represent national outcome averages for the USA and provide reasonable estimates of treatment outcomes following conventional conformal beam radiotherapy. Local tumour control becomes increasingly poor as stage increases with reported rates of tumour local control of 83% for T1, 65–68% for T2 but falling to 44–75% for T3 disease. Tumour size can also influence local control rates. Analysis of the earlier RTOG studies revealing that tumours >25 cm^3 have control rates of less than 50% compared to 75% for <25 cm^3 [25]. The advent of PSA testing led to the realisation that conventional radiotherapy ($\leqslant$70 Gy) gave unsatisfactory results for men with advanced disease. Hanks et al. [26] reported a study of 120 patients followed for a mean of 12.6 years showing biochemical control of only 28% in T3 disease compared to 54% and 72% in T2 and T1 disease [26]. Additionally, high Gleason score correlated with poor outcome with PSA control rates of only 18% for Gleason score 7 and 0% of men with Gleason sum 8 or 9 cancers. More contemporary series using a mean dose of 69 Gy showed 5 year PSA control rates of 81%, 68%, 51% and 31% for men with initial presenting PSA levels of <10, 10–20, 20–<30 and $\geqslant$30 ng/ml respectively [27].

It is clear from these results that for men with bulky local disease, high grade cancers or PSA levels >20 ng/ml that conventional dose radiotherapy alone gives poor long term disease control and strategies to improve outcome are required. Randomised controlled trials have given us important information documenting how improved radiotherapy technique permits higher doses of radiation to be safely delivered, on the value of either short course or longer treatment with adjuvant hormonal therapy and the use of pelvic as well as prostate radiotherapy to improve results in patients with advanced disease. (Table 1).

Radiation dose escalation using conformal or intensity modulated techniques

Over the last 15 years, radiotherapy technology has advanced considerably. The high dose radiation volume can be shaped much more precisely around the prostate and surrounding structures using conformal radiotherapy methods (CFRT). The usual dose limiting toxicity of radiation is proctitis and in a study undertaken at the Royal Marsden Hospital and Institute of Cancer Research, the rate of Grade 2 or more complications was reduced from 15% to 5% using CFRT rather than conventional radiotherapy techniques [28]. This result has given the foundation for subsequent dose escalation studies using CFRT or intensity modulated radiotherapy (IMRT) techniques.

Radiation dose is an independent determinant of biochemical outcome following prostate radiotherapy in several large series [43–48]. However, the patients receiving higher doses were treated more recently than those receiving conventional doses, and the stage and grade migration that have been observed in recent years are important confounding factors in such retrospective analyses. The trend towards a more favourable case mix has contributed to improvements in the outcome of both radiotherapy and of prostatectomy over the last 10 years, even within defined prognostic groups [49]. Confirmation that dose escalation does improve biochemical control rates comes from the results of the MD Anderson randomised trial conducted between 1993 and 1998 [29]. Over 300 men with localised prostate cancer (T1–T3) received radical radiotherapy to the prostate and seminal vesicles and were randomised to either conventional dose (70 Gy) or high dose (78 Gy) treatment. With a median follow up of 60 months, the biochemical control rates for the 70 and 78 Gy arms at 6 years were 64% and 70%,

Table 1
Randomised controlled trials comparing different radiotherapy techniques, doses, fractionation schedules, target volumes and in combination with hormonal therapy

Trial	Eligible patients	Radiotherapy ± randomisation	Hormonal treatment ± randomisation	Outcome
Radiotherapy techniques				
RMH/ICR conformal trial [28]	Those having radical RT for prostate cancer	64 Gy/32 fractions, conventional vs conformal	3 months neo-adjuvant and concurrent LHRH agonist	Lower incidence of late rectal side effects in conformal arm
Radiation dose				
MD Anderson Dose escalation trial [29]	T1–T3	70 vs 78 Gy to prostate	No hormonal treatment	Better freedom from failure in high dose arm for intermediate and high risk patients. Greater rectal toxicity in high dose arm
ICR/RMH dose escalation trial [30]	T1b–T3b N0 M0	74 Gy vs 64 Gy, 1.5 vs 1 cm margin	3 months neo-adjuvant and concurrent LHRH agonist	Suggestion of improved freedom from failure in high dose arm, greater rectal toxicity. Reduced margin reduces toxicity without compromising freedom from failure
Radiotherapy fractionation				
Yeoh [31]	T1–T2, PSA <80 ng/l	64 Gy/32 vs 55 Gy/20 to prostate and base SV, non-conformal	none	After 4 years median follow up no difference in PSA control, slight excess rectal bleeding in hypofractionated arm
Lukka [32]	T1–T2	Prostate RT, 66 Gy/33 vs 52.5 Gy/20	none	Comparable late toxicity, failure rate higher in 52.5 Gy arm. Results consistent with low alpha/beta ratio for prostate cancer
Lymph node irradiation				
RTOG 75-06 [33]	Stage C or Stage A.2-B with pelvic nodal involvement	Pelvis and prostate vs pelvis prostate and para-aortic RT	No hormonal treatment	No difference
RTOG 77-06 [34]	Stage A and B	Prostate only vs prostate and pelvis	No hormonal treatment	No difference
RTOG 94-13 [35]	Localised disease. Lymph node risk ⩾15%. PSA <100	Pelvic vs prostate only RT	2 months MAB: neo-adjuvant and concurrent vs adjuvant	Superior PFS for whole pelvis RT and neoadjuvant/concurrent MAB compared to other treatment combinations

continued on next page

Table 1, *continued*

Trial	Eligible patients	Radiotherapy ± randomisation	Hormonal treatment ± randomisation	Outcome
Hormone therapy and radiation				
RTOG 86-10 [36]	Bulky T2–T4, N0-1	Pelvic and prostate RT	MAB for 4 months neoadjuvant and concurrent vs no hormones	Improvement in all endpoints except overall survival for whole group in hormones arm. Preferential effect of hormones in Gleason $\leqslant$6 subgroup in which there was a survival advantage.
Canadian [37]	T2 or T3	Prostate only RT	RT alone vs 3 months neoadjuvant AS vs 10 months NA,C and A AS	Superior biochemical control in arms including hormones compared to RT alone. No difference between two durations of hormonal treatment
D' Amico [38]	PSA 10–40, Gleason>6 or extracapsular disease on imaging	70 Gy to prostate in two phases	6 months MAB starting 2 months pre radiotherapy vs no hormonal therapy	Improved overall survival in hormonally treated arm
TROG 96-01 [39]	$\geqslant$T2B	Prostate 66 Gy	No hormonal therapy vs 3 months vs 6 months neo-adjuvant and concurrent MAB	MAB improved urinary symptoms pre-RT and had no long term effect on sexual function. Efficacy data awaited
RTOG 92-02 [40]	T2c–T4	Prostate and pelvic RT	4 months neoadjuvant and concurrent MAB vs additional 24 months adjuvant MAB	Superior PFS but not OS in long term arm. Survival advantage in subset with Gleason 8–10 histology
EORTC 22863 [41]	T3–4 and/or any high grade	Pevic and prostate RT	3 yrs concurrent and adjuvant goserelin vs no adjuvant hormones	Improvement in overall and disease free survival in adjuvant hormone arm.
Swedish [42]	Node positive	Pelvis and prostate RT	Orchidectomy vs none	Improvement in overall, cause specific and progression free survival

Table 2
Phase III randomised controlled trials of high dose conformal radiotherapy in prostate cancer

Trial group	No. of patients	Status	Dose
MD Anderson	305	Reported	70 vs 78 Gy
ICR/RMH: Pilot	126	Reported	64 vs 74 Gy (+LHRHa)
MRC RT01	850	Completed	64 vs 74 Gy (+LHRHa)
NKI	600	Completed	68 vs 78 Gy (+LHRHa)
France FNC LCC	300	Completed	70 vs 78 Gy
Mass/Loma Linda	393	Completed	70 vs 78 Gy
RTOG	1520	Commenced	72 vs 78 Gy

respectively ($p=0.03$). Subgroup analysis suggested that the benefit of dose escalation was greater for those with a pretreatment PSA >10 ng/ml. In this subgroup the biochemical control rate was 43% for those who received 70 Gy versus 62% for the 78 Gy arm ($p=0.01$).

A recently reported phase III pilot study of dose escalation undertaken at the Royal Marsden Hospital/ Institute of Cancer Research showed broadly similar results. 126 men were randomised and treated with radiotherapy using either 74 Gy or 64 Gy following 3–6 months of initial androgen suppression. 5 year PSA control was 71% in the 74 Gy group compared to 59% in the 64 Gy group ($p=0.1$) and the hazard ratio for failure was 0.64 in favour of the high dose treatment group ($p=0.1$). The median PSA in this trial was 14 ng/ml and 71% of patients had a moderate or high risk of seminal vesicle involvement [30]. Although there was improved biochemical control in both of these studies, side effects of treatment were also increased, Grade 2 or more rectal toxicity increasing from 12% to 26% in the MD Anderson and from 11% to 18% in the RMH/ICR trial. Preliminary results for a trial combining external beam radiotherapy to the prostate and seminal vesicles (50.4 Gy) plus a proton beam boost of either 19.8 or 28.8 Gy equivalent have recently been reported in a group of 393 patients [50]. Overall, there was an 18% improvement in 5 year biochemical failure rates (increasing from 63% to 81%, $p=0.00001$). This difference held true for both low or intermediate risk disease. Morbidity in this trial was very low. None of these three trials has, as yet, sufficient follow up to show that improved biochemical control necessarily translates into an impact on overall survival. However, a retrospective analysis from the RTOG which included 1465 men treated between 1975 and 1992 found that men treated with high grade cancer who received higher radiation doses ($\geq$66 Gy versus <66 Gy) had a 27% increase in overall mortality.

Over 3000 men will be randomised in ongoing phase III studies of dose escalation (Table 2) in the UK (MRC RT01 trial) [51], the Netherlands, France and North America and together these will give very much more accurate information on the relative advantages of dose escalation in different risk groups. However, currently, dose escalation seems to be most certainly of benefit in those patients with more advanced or high grade presentations.

Radiobiology and fractionation studies in prostate cancer

Estimation of the alpha/beta ratio for prostate cancer from brachytherapy series suggests the value may be low ($\leq$1.5 Gy) [52–56] although this remains controversial [57]. A recent review suggests that the alpha/beta ratio for radiation induced proctitis may be relatively high at 5.4 Gy [58]. These two estimates for tumour and late normal tissues suggest that hypo-fractionated treatments may confer a therapeutic advantage.

A phase III trial in 936 men has compared 52.5 Gy in 20 fractions with 66 Gy in 33 fractions. Preliminary results show a 7% reduction in PSA control rate (49% vs 56%) in the 20 fraction arm with hazard ratio for failure (short to long) of 1.20 (95%CI: 1.0–1.44). Late toxicity was similar in the two arms (Grade 3/4 = 3%) [32]. A second, small, RCT including 120 men compared a dose of 64 Gy in 32 fractions with 55 Gy in 20 fractions. After a median follow up of 44 months, 4 year PSA control rates were similar (86.2%/85.4% for hypo and standard fractionation respectively); there was a slight excess of rectal bleeding in the hypofractionated group [31]. Comparison of a large single institute series in which 705 men were treated to a dose of 50 Gy in 16 fractions gave similar PSA control rates to schedules of 65–70 Gy in 1.8–2.0 Gy fractions with a low toxicity profile [59]. All of these studies are compatible with an alpha/beta ratio for prostate cancer of $\leq$1.5. In the pre-PSA era, 36 Gy in 6 fractions in 3 weeks was reported as giving acceptable results without major early or late morbidity [60]. Presently there is no long term data using higher dose hypofractionated radiotherapy, a preliminary report from the USA [61] suggested that a dose of 70Gy in 2.5Gy fractions was at least as effective as 78 Gy in 2 Gy fractions. Phase I studies using 3 Gy fractions have recruited in Manchester (57 Gy, 60 Gy) [62], Toronto (up to 66 Gy)

Table 3
Target volumes for trials using high dose conformal radiotherapy[a]

Trial	SV involvement Risk[b] (%)	Target + Margin (mm)[c]			Dose[d] (Gy)			
		Phase I	Phase II	Phase III	Phase I	Phase II	Phase III	Total
Dutch	Low (<10)	P + 10	P + 5/0	–	68	0,10	–	68, 78
	Mod (10–25)	P + SV + 10	P + 10	P + 5/0	50	18	0,10	68, 78
	High (>25)	P + SV + 10	P + 5/0	–	68	0,10	–	68, 78
	Involved	P + SV + 10	P + SV + 5/0	–	68	0,10	–	68, 78
Protect	Low (<15)	P+bSV+10/5	P + 0	–	56	18	–	74
	High (⩾15)	P + SV	P + 0	–	56	18	–	74
RT 01	Low (<15)	P + bSV + 10	P + 0	–	64	0,10	–	64, 74
	High (⩾15)	P + SV	P + 0	–	64	0,10	–	64, 74
EORTC 22991	All	P + SV + 10 ± Nodes	P + bSV + 10	P + 5/0	46	24	0, 4, 8	70, 74, 78 (not randomised)
RTOG P-0126	All	P + SV + 10/5	P + 10/5	–	58	15, 24	–	73, 82
RTOG 9406	Low (<15)	P + 5–10	P + 5–10	–	68	0, 6, 11	–	68, 74, 79
	High (⩾15)	P + SV + 5–10	P + 5–10	–	56	12, 8, 23	–	68, 74, 79
	Involved	P + SV + 5–10	–	–	68, 74, 79	–	–	68, 74, 79
MSKCC	All	P + SV + 10/6	P + SV + 10/6 Rectal block	–	65, 70, 76, 76	0, 0, 0, 5	–	65, 70, 76, 81
CHHIP[e]	Low (<15)	P + bSV + 10	P + 10/5	P+5/0	56	16	4	74
	High (⩾15)	P + SV + 10	P + 10/5	P+5/0	56	16	4	74

[a] SV: Seminal Vesicle; bSV: base of Seminal Vesicle; P: Prostate.
[b] Risk of SV based on Roach formula and Partin tables.
[c] ' /' indicates margin: all around prostate/prostate–rectum interface.
[d] Multiple figures in each risk group indicate different dose arms of trials.
[e] Conventionally fractionated arm.

and Japan (69 Gy) [63] and a phase III randomised trial (CHHIP) is recruiting in the UK comparing 74 Gy in 2 Gy fractions with 60 and 57 Gy in 3 Gy fractions. If these trials show an equivalence or an advantage for the shorter fractionation schedules, then this would not only be more convenient for patients but make better use of radiotherapy resource.

Radiotherapy and target margins

The radiotherapy target volume may include the prostate, all or part of the seminal vesicles and pelvic lymph nodes. A ' safety margin' needs to be placed around these structures on CT planning images to allow for microscopic spread of disease, day to day uncertainties in the accuracy of treatment as well as any movement in the structures being treated. A single small study has evaluated the appropriate margin around the prostate using conformal radiotherapy techniques. In this trial, 126 men were randomised to have either a 1.0 cm or 1.5 cm margin. There was no difference in the PSA control rate but the larger margin was associated with a short lasting increase in acute side effects affecting bowel and bladder as well as an increase in late rectal side effects with ⩾ Grade 2 toxicity being recorded in 21% of patients compared to 13% ($p = 0.05$) [30]. It therefore seems that margins of more than 1 cm are unnecessary and should not be used. Some trial protocols now specify a reduced posterior margin so as to keep the dose to rectum as low as possible [64]. This is particularly important if using high dose treatments. Doses and margins used in current protocols are summarised in Table 3.

Seminal vesicles (SV) are included in the treatment volume if they are clinically or radiologically involved. They are also frequently treated if they are at a high risk of being microscopically involved based on the Roach formula (risk of seminal vesicle invasion = PSA + [(Gleason score − 6) × 10]) [65]. No studies have been undertaken to evaluate the clinical benefit from including seminal vesicles within the target volume but unless the seminal vesicles are specifically outlined, they are not reliably included in the high dose volume [66]. Pathological data [67] has suggested 3 patterns of seminal vesicle invasion: (i) tumour spread along ejaculatory ducts, 35% of cases; (ii) direct extension through capsule, 61%

of cases; and (iii) the presence of isolated tumour deposits, 12% of cases. One series [68] showed that the median distance from the prostate of seminal vesicle invasion was 1 cm and that in 90% of cases, involvement was limited to the proximal 2 cm. They advocate including the proximal 2.0 cm in the CTV when it is desired to treat the seminal vesicles. Davis et al. [69] however found that tumour was found within 0.5 cm of the tip of the seminal vesicles in 40% of patients with seminal vesicle involvement, and advocated treating the seminal vesicles in their entirety. Our practice is to include the entire seminal vesicles for stage T3 tumours, or if the risk of seminal vesicle involvement is >15%, provided that the predicted dose to rectum is acceptable. If the rectal dose is unacceptable then the tips of the seminal vesicles are excluded, but we treat the proximal 2 cm. Strategies for including the seminal vesicles in current trials are shown in Table 3.

Pelvic radiotherapy is frequently used in patients with locally advanced prostate cancer but evidence for benefit has, until recently, been lacking although some retrospective studies have shown a potential advantage [70]. The only previous randomised trial performed by the RTOG in the pre-PSA era in patients with T1 and T2 cancers failed to show an advantage for lymph node irradiation [34] and without evidence of benefit, many clinicians omitted whole pelvic irradiation in view of its high risk of complications. RTOG trial 94-13 [35] recruited 1323 patients who had an estimated risk of lymph node involvement of $\geqslant$15%. Patients were randomly assigned to whole pelvic radiotherapy or prostate only treatment with a second randomisation to 4 months neoadjuvant or adjuvant androgen suppression. After a five year follow up pelvic radiotherapy was associated with a 4 year progression free survival of 54% compared with 47% in patients treated with prostate only radiotherapy ($p = 0.02$). It is not yet certain that this progression free difference will translate into an overall survival benefit. A detailed analysis of the toxicity of pelvic radiotherapy in this trial is not yet available. However, the benefit of pelvic radiotherapy seems similar to that of regional lymph node irradiation in breast cancer [71]. In general, the use of lymph node irradiation is limited to between 44 and 50 Gy to avoid side effects which is probably a sub-optimal dose to destroy micrometastases. Pre-clinical studies have shown that IMRT techniques can substantially reduce the bowel and bladder volume irradiated during pelvic radiotherapy. Bowel and colon irradiated to the 90% isodose level is reduced from 24% using convenional radiotherapy to 18% using conformal techniques but only 5% reaches this dose level using IMRT [72]. Subsequently, the Royal Marsden Hospital group have developed a phase I/II trial of dose escalated pelvic lymph node irradiation. Preliminary results show low levels of both acute and late toxicity with target lymph node doses of 50, 55 and 60 Gy [73]. Further follow-up and studies will be required to confirm the low level of toxicity and potential benefit.

Technological advances in imaging, tumour localisation, treatment planning, delivery of complex CFRT and IMRT treatments as well as improvements in verification and the accuracy of treatment using, for example, portal imaging devices potentially leads to more effective and safer treatments [74]. It is now clear that dose volume complication relationships exist and these have been most well demonstrated for rectal toxicity. Although different groups of researchers have used different methodologies, it is possible to draw up guidelines and dose constraints for rectum, bladder and bowel [29,75–84]. Table 4 shows the dose constraints currently in use at the Royal Marsden Hospital and for the on-going trial of high dose hypofractionated radiotherapy (CHHIP).

Table 4
Normal tissue dose constraints

	Dose for 2 Gy/# Prescribed dose	Dose (%)	Max vol (% or cc)
Rectum	50	68	60%
	60	81	50%
	65	88	30%
	70	95	15%
	74	100	3%
Bladder	50	68	50%
	60	81	25%
	74	100	5%
Femoral heads	50	68	50%
Bowel	50	68	17cc

Brachytherapy and external beam radiotherapy

An alternative strategy is to combine brachytherapy with external beam radiotherapy to produce a high dose conformal boost. Brachytherapy may be given using either low dose rate permanent seed implants with Iodine-125 or Palladium-103 or high dose rate temporary implants with Iridium-192. The fall off in dose from the implanted sources is rapid following an inverse square law so that treatment of extra capsular disease is unreliable. Monotherapy brachytherapy is,

therefore, suitable for good risk patients only where long term results are similar to those of prostatectomy or external beam radiotherapy [85–88]. The Seattle Group have used Iodine-125 seeds to give an implant dose of 120 Gy with pelvic external beam radiotherapy to a dose of 45 Gy in 25F [87]. The Mount Sinai Group have treated high risk patients [PSA >15 ng/ml, Gleason ⩾8, T2c–T3) with implant, pelvic radiotherapy and nine months of androgen suppression achieving 86% biopsy negative results at two years and also 86% freedom from biochemical failure at 5 years [88,89]. Critz and colleagues [90] have followed seed implantation by external beam irradiation and report 10 year disease free survival (PSA <0.2 ng/ml) of 61% for men with high risk features at presentation. Morbidity in these studies has generally been low [91] and in a recent matched pair analysis late rectal toxicity was decreased by 15% using Palladium-103 seeds and external beam radiotherapy in comparison to external beam radiotherapy alone with similar late genito-urinary side effects [92]. However, Sarsody [93] reported a significantly higher rate of side effects using combined modality treatments compared to brachytherapy alone including need for TURP (5% vs 14.5%, $p=0.03$), rectal bleeding (15.5% vs 36%, $p=0.002$) and the need for faecal (7%) or urinary diversion (3%) neither of which were recorded after brachytherapy alone. Such data reinforce the caution that is needed and strict adherence to quality assurance and technique when using combined modality treatments.

High dose rate brachytherapy potentially takes advantage of the low alpha-beta ratio or prostate cancer (see above). Combined therapies usually use external beam radiotherapy to a dose of 46–50 Gy but have used a range of brachytherapy dose and treatment fractionation [94–97] which may be interdigitated during the external beam radiotherapy treatment. In a multi-institute review [95] 359 high risk patients were treated with external beam radiotherapy (46–50 Gy) and high dose rate (HDR) boost of 15 Gy × 2 (Kiel), 3–4 Gy × 3 (Seattle) or 5.5 Gy × 4/11 Gy × 2 (William Beaumont). Results were similar from the different institutions with a PSA control rate of 69% at 5 years and 95% cause specific survival. The Michigan Group [96] have enrolled 207 men in dose escalation trials using 5.5 Gy × 3 to 11.5 Gy × 3 interdigitated with external beam radiotherapy to a dose of 46 Gy. For intermediate and high risk patients, 5 year PSA control was 74% overall and 50% for the highest risk group. Results appeared to improve with higher doses. Grade 3 or more genito-urinary and rectal side effects were reported in 8% and 1% of men respectively. Broadly similar results have been obtained by Brazilian and Swedish Groups. Pellizzon and colleagues [97] describe a 74% 4 year biochemical control rate for intermediate/high risk patients with 12% and 5% Grade 1–2 genito-urinary and bowel toxicity respectively using external beam radiotherapy to 45 Gy and HDR of 4–5 Gy × 4. Astrom and colleagues [94] report a 61% 5 year PSA control rate for intermediate/high risk patients using 50 Gy external beam radiotherapy and HDR of 10 Gy × 2F. Moderate genito-urinary complications were seen in 36% of men and gastro-intestinal side effects in 17%. There have been no randomised comparisons between these combined modality treatments and high dose external beam radiotherapy alone - both are satisfactory ways of delivering high dose treatment and the choice is principally dependent on local facilities, skills and interest. Randomised trials are required and have been initiated in the UK [98].

Use of neoadjuvant and adjuvant hormonal therapy in combined modality treatment with radiotherapy

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 EORTC trial 22863 by Bolla and colleagues in 1997 [99]. Since then our understanding of the appropriate use of hormone therapy as an adjuvant to radiation has been informed by the results of several important randomised trials using short course neoadjuvant (approx 6 months) or longer courses (⩾2 years) of adjuvant androgen suppression.

Short course or neoadjuvant androgen suppression

RTOG 86-10 randomised 470 men with locally advanced disease to radiotherapy with or without 4 months neoadjuvant total androgen suppression [36]. 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% versus 44%, $p=0.10$). A statistically significant survival advantage was seen in the subgroup of 129 men with Gleason 2–6 disease, in whom 8-year overall survival was 70% for combined treatment versus 52% for radiation alone ($p=0.015$). More recently a Canadian trial comprising 481 men with T2–3 disease [37] has shown a benefit of short course neoadjuvant androgen deprivation

prior to radiotherapy as compared to radiotherapy alone with 7 year biochemical failure free survival of 66% with hormones compared to 42% without ($p < 0.01$). In this study there was no advantage for the 12 month rather than 6 month course of androgen suppression. D' Amico and colleagues [38] randomised 206 patients with intermediate or high risk localised disease between radiotherapy alone and radiotherapy and a 6 month course of androgen suppression starting 2 months before radiotherapy. After a median follow-up of 5 years, an overall survival advantage was seen with the addition of hormonal treatment (88% vs 78% $p = 0.04$) with an increase in 5 year survival free of salvage rate from 57% to 82% ($p = 0.002$) with the addition of hormonal treatment. The optimal timing of short course hormonal therapy has been addressed in RTOG study 94-13 [35]. In this study, patients with an estimated risk of lymph node involvement of $\geqslant 15\%$ were randomised to 4 months androgen suppression either before and during or after radiotherapy. There was an advantage for the initial hormone treatment approach in men who additionally had pelvic irradiation. The acceptability of short term androgen suppression has been assessed in a substantial Australian trial undertaken in over 900 men [39]. In this study, men were randomised to receive no hormonal therapy, or 3 or 6 months of maximal androgen blockade. It was noted that maximal androgen blockade improved urinary symptoms prior to radiotherapy and that sexual functioning was similar in all three randomised groups one year after treatment. It is important to note that following short course androgen suppression testosterone levels are expected to recover to normal in almost all men 6–12 months post treatment [100].

Short versus long course androgen suppression

Is there an additional benefit for long-term rather than short-term adjuvant hormone therapy? This issue was addressed by RTOG 92-02, in which over 1500 men with locally advanced disease (T2c–T4) all received radical radiotherapy with 4 months of neoadjuvant total androgen suppression, and were randomly allocated to an additional 2 years of adjuvant Goserelin or to observation [40]. Overall, the duration of adjuvant hormone therapy had no effect on survival. Five-year overall survival was 78% versus 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 5-year overall survival of 80% versus 69% ($p = 0.02$). Although there is a significant downside to the use of long-term (rather than short-term) adjuvant hormone therapy, the absolute overall survival benefit of approximately 10% at 5 years for this subgroup, will, for most men, outweigh the detrimental effects on quality of life.

Should long-term adjuvant hormone therapy also be considered for men with Gleason scores $\leqslant 7$? Closer analysis of the RTOG 92-02 abstract suggests not: Approximately 1200 men had a Gleason score $\leqslant 7$, and in this group not only was there no survival benefit for long-term Goserelin, there was actually a trend towards a survival detriment. Although 5-year disease-specific survival was improved by approximately 3% (estimated at 92.5% versus 89.5%), this was more than outweighed by the estimated 7% increased risk of death from causes other than prostate cancer (15% versus 8%) [101]. It has previously been suspected that long-term LHRH analogue therapy could be linked with an excess of non-prostate cancer deaths [102]. 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 [103] and LHRH agonist therapy leads to both increased insulin resistance and arterial stiffness [104]. At present, it is uncertain whether long-term LHRH agonist therapy significantly increases non-prostate cancer mortality, but because it is a distinct possibility it follows that its use as an adjuvant to radiotherapy should be restricted to patient groups in which it has been demonstrated to have an overall survival benefit. It also follows that future clinical trials of adjuvant therapy should use overall, and not disease-specific, survival as the main endpoint.

Long course androgen suppression

In EORTC trial 22863 405 men with T3–4 and/or high grade prostate cancer were randomly assigned to receive pelvis and prostate radiotherapy alone or radiotherapy plus concurrent and adjuvant Goserelin for 3 years [41]. The five year overall survival was significantly better in the combined treatment arm (79%, CI: 72%-86%) compared with the radiotherapy alone arm (62%, CI: 52%–72%). In RTOG 85–31, 977 men with T3 and/or N1 disease were randomised to radiotherapy alone or the addition of long term adjuvant hormonal therapy which started at the end rather than at the beginning of radiotherapy. Initial results showed a statistically significant cause specific and overall survival advantage in favour of the combined treatment arm in the sub-group of patients with Gleason 8–10 tumours, but updated

Table 5
Radiotherapy alone or with long term androgen suppression [41,105,106,42]

	EORTC 22863 5 yr actuarial results	RTOG 85-31 10 yr actuarial results	Swedish Trial 9 yr crude results
Freedom from local recurrence	84% vs 98% ($p \leqslant .0001$)	61% vs 77% ($p \leqslant .0001$)	
Freedom from distant metastases	71% vs 90% ($p \leqslant .0001$)	61% vs 75% ($p \leqslant .0001$)	
Freedom from PSA failure	45% vs 76% ($p \leqslant .0001$)	9% vs 30% ($p \leqslant .0001$)	
Clinical progression free survival	40% vs 74% ($p \leqslant .0001$)		56% vs 73% ($p = 0.06$)
Cause specific survival	79% vs 94% ($p \leqslant .0001$)	78% vs 83% ($p \geqslant .005$)	71% vs 90% ($p = 0.02$)
Overall survival	62% vs 78% ($p \leqslant .0001$)	38% vs 53% ($p = 0.0004$)	71% vs 90% ($p = 0.005$)

results show this effect now extends to the entire study population (53% vs 38%, $p = 0.004$) [105,106]. In a small Swedish trial [42] men with lymph node positive disease were randomised to radiotherapy with or without orchidectomy and those treated with castration had a 69% compared to 39% improved overall survival rate ($p = 0.005$). The magnitude in the differences of outcome in these trials could relate to the timing of hormone treatment in relation to radiotherapy but is probably also determined by the mix of patients entering the studies and perhaps the timing of salvage treatment for those who develop biochemical failure of disease. Nevertheless, it is clear from these three completed randomised studies using long term androgen suppression that there are clinically significant advantages for patients with locally advanced and high grade or node positive cancers not only in biochemical control of disease but also freedom from distant metastases as well as cause specific and overall survival (Table 5) [41,105,106,42]. Currently the separation of patients into those groups who should receive shorter rather than longer course hormonal therapy remains somewhat unclear. RTOG trial 99-10 is recruiting men with intermediate or high risk localised disease (target accrual 1540) and comparing 4 vs 8 months of total androgen suppression prior to and during radiotherapy. RTOG trial 99-02 is recruiting high risk patients (target accrual 1440) comparing initial and adjuvant hormonal therapy with irradiation to the same treatment but with 4-cycles of chemotherapy. Whilst it may be likely that more aggressive combined modality treatment schedules may benefit younger men with prostate cancer, it should be appreciated that for many more elderly men androgen suppression alone may remain the treatment of choice.

Conclusions

If radiotherapy is used in the management of patients with locally advanced cancer, evidence from reported randomised control trials suggest 2–3 years of adjuvant hormonal therapy should be given to men with high grade (Gleason 8–10) or node positive cancers. Short course hormonal therapy (3–6 months) should be considered for all others although the relative benefits of short course androgen suppression and dose escalated radiotherapy remain to be fully defined for those patients with intermediate risk disease. Recovery of androgen levels following short course hormone therapy is to be expected and it is not yet certain whether such treatment or dose escalation will have more long term morbidity particularly related to erectile dysfunction. It also remains to be determined whether radiotherapy and long term (2–3 years) androgen suppression has more or less morbidity than permanent androgen suppression.

References

1 Zelefsky MJ, Leibel SA, Gaudin PB, *et al.* Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998, **41**(3), 491–500.
2 Zelefsky MJ, Moughan J, Owen J, Zietman AL, Roach M 3rd, Hanks GE. Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 Patterns of Care survey for prostate cancer. *Int J Radiat Oncol Biol Phys* 2004, **59**(4), 1053–61.
3 D' Amico AV, Whittington R, Malkowicz SB, Schultz D,*et al.* Biochemical outcome after radical prostatectomy, external beam radiation therapy or interstitial radiation therapy for clinically localised prostate cancer. *JAMA* 1998, **280**(11), 969–974.
4 Husband JE, Johnson RJ, Reznek RH. *A Guide to the Practical Use of MRI in Oncology*. London, The Royal College of Radiologists, 1999.

5 Albertsen PC, Hanley JA, Harlan LC, *et al*. The positive yield of imaging studies in the evaluation of men with newly diagnosed prostate cancer: a population based analysis. *J Urol* 2000, **163**(4), 1138–43.

6 Allen DJ, Hindley R, Clovis S, *et al*. Does body-coil magnetic-resonance imaging have a role in the preoperative staging of patients with clinically localized prostate cancer? *BJU Int* 2004, **94**(4), 534–8.

7 Jackson AS, Parker CC, Norman AR, *et al*. Tumour staging using magnetic resonance imaging in clinically localised prostate cancer: relationship to biochemical outcome after neo-adjuvant androgen deprivation and radical radiotherapy. *Clin Oncol (R Coll Radiol)* 2005, **17**(3), 167–71.

8 Coakley FV, Qayyum A, Kurhanewicz J. Magnetic resonance imaging and spectroscopic imaging of prostate cancer. *J Urol* 2003, **170**(6Pt2), S69–75; discussion S75-6.

9 Hara N, Okuizumi M, Koike H, Kawaguchi M, Bilim V. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a useful modality for the precise detection and staging of early prostate cancer. *Prostate* 2005, **62**(2), 140–7.

10 Roach III M. Re: The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer [letter; comment]. *J-Urol* 1993, **150**(6), 1923–4 issn: 0022-5347.

11 Vinnicombe SJ, Norman AR, Nicolson V, Husband JE. Normal pelvic lymph nodes: evaluation with CT after bipedal lymphangiography. *Radiology* 1995, **194**(2), 349–55.

12 Borley N, Fabrin K, Sriprasad S, *et al*. Laparoscopic pelvic lymph node dissection allows significantly more accurate staging in "high-risk" prostate cancer compared to MRI or CT. *Scand J Urol Nephrol* 2003, **37**(5), 382–6.

13 Heidenreich A, Varga Z, Von Knobloch R. Extended pelvic lymphadenectomy in patients undergoing radical prostatectomy: high incidence of lymph node metastasis. *J Urol* 2002, **167**(4), 1681–6.

14 Golimbu M, Morales P, Al-Askari S, Brown J. Extended pelvic lymphadenectomy of prostatic cancer. *Journal of Urology* 1979, **121**(5), 617–620.

15 Kim JY, Harisinghani MG. MR imaging staging of pelvic lymph nodes. *Magn Reson Imaging Clin N Am* 2004, **12**(3), 581–6.

16 Harisinghani MG, Saini S, Weissleder R, *et al*. MR lymphangiography using ultrasmall superparamagnetic iron oxide in patients with primary abdominal and pelvic malignancies: radiographic-pathologic correlation. *AJR Am J Roentgenol* 1999, **172**(5), 1347–51.

17 NHS NICE Guidance on Cancer Services: Improving Outcomes in Urological Cancers – The Manual; 2002.

18 Freedman GM, Negendank WG, Hudes GR, Shaer AH, Hanks GE. Preliminary results of a bone marrow magnetic resonance imaging protocol for patients with high-risk prostate cancer. *Urology* 1999, **54**(1), 118–23.

19 Hanks GE. Treatment of early stage prostate cancer: radiotherapy. In: DeVita VT, Hellman S, Rosenberg SA (editors). *Important Advances in Oncology*. Philadelphia, J.B. Lippincott Company, 1994. p.225–239.

20 Hanks GE, Hanlon A, Owen JB, Schultheiss TE. Patterns of radiation treatment of elderly patients with prostate cancer. *Cancer* 1994, **74**(Supplto7), 2174–2177.

21 Goffinet DR, Baghaw MA. *Radiation therapy of prostate carcinoma: thirty year experience at Stanford University. Treatment of prostatic cancer – facts and controversies*. Wiley-Liss Inc, 1990.

22 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**(7), 1489–1499.

23 Zagars GK, Von Eschenbach AC, Johnson DE, Oswald JM. The role of radiation therapy in stages A2 and B adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1988, **14**, 701–709.

24 Perez CA, Pilepich MV, Garcia D, Simpson JR, Zivnuska F, Hederman MA. Definitive radiation therapy in carcinoma of the prostate localized to the pelvis: experience at the Mallinckrodt Institute of Radiology. *NCI Monogr* 1988(7), 85–94.

25 Pilepich MV, Krall JM, Sause WT, *et al*. Prognostic factors in carcinoma of the prostate-analysis of RTOG study 7506. *Int J Rad Oncol Biol Phys* 1987, **13**(3), 339–49.

26 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 Clinical Oncol* 1996, **14**(4), 1093–1097.

27 Shipley WU, Thames HD, Sandler HM, *et al*. Radiation therapy for clinically localised prostate cancer: a multi-institutional pooled analysis. *JAMA* 1999, **281**(17), 1598–1604.

28 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.

29 Pollack A, Zagars GK, Starkschall G, *et al*. Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002, **53**(5), 1097–105.

30 Dearnaley DP, Hall E, Lawrence D, *et al*. Phase III pilot study of dose escalation using conformal radiotherapy in prostate cancer: PSA control and side effects. *Br J Cancer* 2005, **92**(3), 488–98.

31 Yeoh EE, Fraser RJ, McGowan RE, *et al*. Evidence for efficacy without increased toxicity of hypofractionated radiotherapy for prostate carcinoma: early results of a Phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2003, **55**(4), 943–55.

32 Lukka H, Hayter C, Warde P, *et al*. A randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2003, **57**(2Suppl), S126.

33 Pilepich MV, Krall JM, Johnson RJ, *et al*. Extended field (periaortic) irradiation in carcinoma of the prostate analysis of RTOG 75-06. *Int J Radiat Oncol Biol Phys* 1986, **12**(3), 345–51.

34 Asbell SO, Krall JM, Pilepich MV, *et al*. Elective pelvic irradiation in stage A2, B carcinoma of the prostate: Analysis of RTOG 77-06. *Int J Radiat Oncol Biol Phys* 1988, **15**(6), 1307–1316.

35 Roach III M, 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**(10), 1904–11.

36 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**(5), 1243–52.

37 Laverdiere J, Nabid A, De Bedoya LD, *et al*. The efficacy and sequencing of a short course of androgen suppression

on freedom from biochemical failure when administered with radiation therapy for T2–T3 prostate cancer. *J Urol* 2004, **171**(3), 1137–40.

38 D' Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004, **292**(7), 821–7.

39 Lamb DS, Denham JW, Mameghan H, *et al*. Acceptability of short term neo-adjuvant androgen deprivation in patients with locally advanced prostate cancer. *Radiother Oncol* 2003, **68**(3), 255–67.

40 Hanks GE, Pajak TF, Porter A, *et al*. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003, **21**(21), 3972–8.

41 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**(9327), 103–6.

42 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(6), 2030–4 issn: 0022-5347.

43 Fiveash JB, Hanks G, Roach M, *et al*. 3D conformal radiation therapy (3DCRT) for high grade prostate cancer: a multi-institutional review. *Int J Radiat Oncol Biol Phys* 2000, **47**(2), 335–42.

44 Hanks GE, Hanlon AL, Schultheiss TE, *et al*. Dose escalation with 3D conformal treatment: five year outcomes, treatment optimization, and future directions. *Int J Radiat Oncol Biol Phys* 1998, **41**(3), 501–10.

45 Michalski JM, Purdy JA, Winter K, *et al*. Preliminary report of toxicity following 3D radiation therapy for prostate cancer on 3DOG/RTOG 9406. *Int J Radiat Oncol Biol Phys* 2000, **46**(2), 391–402.

46 Sandler HM, Perez-Tomayo C, Ten Haken RK, Lichter AS. Dose escalation for stage C (T3) prostate cancer: minimal rectal toxicity observed using conformal therapy. *Radiotherapy and Oncology* 1992, **23**(1), 53–54.

47 Zelefsky MJ, Cowen D, Fuks Z, *et al*. Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. *Cancer* 1999, **85**(11), 2460–8.

48 Zelefsky MJ, Fuks Z, Hunt M, *et al*. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol* 2001, **166**(3), 876–81.

49 D' Amico AV, Chen MH, Oh-Ung J,*et al*. Changing prostate-specific antigen outcome after surgery or radiotherapy for localized prostate cancer during the prostate-specific antigen era. *Int J Radiat Oncol Biol Phys* 2002, **54**(2), 436–41.

50 Rossi C, Zietman AL, DeSilvio M, *et al*. A randomised trial comparing conventional dose (70.2 GyE) and high dose (79.2 GyE) conformal radiation in early stage adeno-carcinoma of the prostate: Results of an intermi analysis of PROG 95-09. In: Grunberg SM, editor. *Multidisciplinary Prostate Cancer Symposium*, 2005, Orlando, Florida, UK: American Society of Clinical Oncology; 2005, p.AbstractNo58.

51 Sydes MR, Stephens RJ, Moore AR, *et al*. Implementing the UK Medical Research Council (MRC) RT01 trial (ISRCTN 47772397): methods and practicalities of a randomised controlled trial of conformal radiotherapy in men with localised prostate cancer. *Radiother Oncol* 2004, **72**(2), 199–211.

52 Amer AM, Mott J, Mackay RI, *et al*. Prediction of the benefits from dose-escalated hypofractionated intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2003, **56**(1), 199–207.

53 Brenner DJ. Toward optimal external-beam fractionation for prostate cancer. *Int J Radiat Oncol Biol Phys* 2000, **48**(2), 315–6.

54 Brenner DJ. Hypofractionation for prostate cancer radiotherapy – what are the issues? *Int J Radiat Oncol Biol Phys* 2003, **57**(4), 912–4.

55 Duchesne GM, Peters LJ. What is the alpha/beta ratio for prostate cancer? Rationale for hypofractionated high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 1999, **44**(4), 747–8.

56 King CR, Fowler JF. A simple analytic derivation suggests that prostate cancer alpha/beta ratio is low. *Int J Radiat Oncol Biol Phys* 2001, **51**(1), 213–4.

57 Nahum AE, Movsas B, Horwitz EM, Stobbe CC, Chapman JD. Incorporating clinical measurements of hypoxia into tumor local control modeling of prostate cancer: implications for the alpha/beta ratio. *Int J Radiat Oncol Biol Phys* 2003, **57**(2), 391–401.

58 Brenner DJ. Fractionation and late rectal toxicity. *Int J Radiat Oncol Biol Phys* 2004, **60**(4), 1013–5.

59 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**(5), 1254–9.

60 Lloyd-Davies RW, Collins CD, Swan AV. Carcinoma of prostate treated by radical external beam radiotherapy using hypofractionation. Twenty-two years' experience (1962–1984). *Urology* 1990, **36**(2), 107–11.

61 Kupelian PA, Reddy CA, Carlson TP, Altsman KA, Willoughby TR. Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy (70 Gy at 2.5 Gy/fraction) for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2002, **53**(4), 904–12.

62 Mott JH, Livsey JE, Logue JP. Development of a simultaneous boost IMRT class solution for a hypofractionated prostate cancer protocol. *Br J Radiol* 2004, **77**(917), 377–86.

63 Akimoto T, Muramatsu H, Takahashi M, *et al*. Rectal bleeding after hypofractionated radiotherapy for prostate cancer: correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding. *Int J Radiat Oncol Biol Phys* 2004, **60**(4), 1033–9.

64 Pickett B, Roach III M, Verhey L, *et al*. The value of nonuniform margins for six-field conformal irradiation of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1995, **32**(1), 211–218.

65 Diaz A, Roach III M, Marquez C, *et al*. Indications for and the significance of seminal vesicle irradiation during 3D conformal radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1994, **30**(2), 323–329.

66 Parker C, Haycocks T, Bayley A, Alasti H, Warde P, Catton C. A dose-volume histogram analysis of the seminal vesicles in men treated with conformal radiotherapy to ' prostate alone' . *Clin Oncol (R Coll Radiol)* 2002, **14**(4), 298–302.

67 Ohori M, Scardino PT, Lapin SL, Seale-Hawkins C, Link J, Wheeler TM. The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. *Am J Surg Pathol* 1993, **17**(12), 1252–61.

68 Kestin L, Goldstein N, Vicini F, Yan D, Korman H, Martinez A. Treatment of prostate cancer with radiotherapy: should the entire seminal vesicles be included in the clinical target volume? *Int J Radiat Oncol Biol Phys* 2002, **54**(3), 686–97.

69 Davis BJ, Cheville JC, Wilson TM, Slezak JM, Pisansky TM. Histopathologic characterisation of seminal vesicle invasion in prostate cancer: implications for radiotherapeutic management. In: Cox JD, editor. *ASTRO 43rd Annual Meeting*, 2001; San Francisco, California, USA: Elsevier Science Inc; 2001. p. Abs250 pp140/1.

70 Seaward SA, Weinberg V, Lewis P, Leigh B, Phillips TL, Roach MR. Improved freedom from PSA failure with whole pelvic irradiation for high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 1998, **42**(5), 1055–62 issn: 0360-3016.

71 Overgaard M. Radiotherapy as part of a multidisciplinary treatment strategy in early breast cancer. *Eur J Cancer* 2001, **37**Suppl7, S33–43.

72 Nutting C, Convery D, Cosgrove V, *et al*. Reduction in 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**(3), 649–656.

73 Guerrero-Urbano MT, Norman A, Adams EJ, *et al*. A phase I dose escalation study of intensity modulated radiotherapy (IMRT) to treat the prostate and pelvic nodes in patients with locally advanced prostate cancer. In: Grunberg SM, editor. *Multidisciplinary Prostate Cancer Symposium*, 2005, Orlando, Florida, UK: American Society of Clinical Oncology; 2005. p. Abstract No 179, P.123.

74 Mangar S, Huddart RA, Parker CC, Dearnaley DP, Khoo VS, Horwich A. Technological advances in radiotherapy for the treatment of localised prostate cancer. *Eur J Cancer* 2005, In press.

75 Fiorino C, Cozzarini C, Vavassori V, *et al*. Relationships between DVHs and late rectal bleeding after radiotherapy for prostate cancer: analysis of a large group of patients pooled from three institutions. *Radioth Oncol* 2002, **64**(1), 1–12.

76 Fiorino C, Sanguineti G, Cozzarini C, *et al*. Rectal dose-volume constraints in high-dose radiotherapy of localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2003, **57**(4), 953–62.

77 Lu Y, Song PY, Li SD, *et al*. A method of analyzing rectal surface area irradiated and rectal complications in prostate conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1995, **33**(5), 1121–5.

78 Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I. Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2000, **48**(3), 635–42.

79 Benk VA, Adams JA, Shipley WU, *et al*. Late rectal bleeding following combined x-ray and proton high dose irradiation for patients with stage T3–T4 prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1993, **26**(3), 551–557.

80 Boersma LJ, van den Brink M, Bruce AM, *et al*. Estimation of the incidence of late bladder and rectum complications after high-dose (70–78 Gy) conformal radiotherapy for prostate cancer, using dose-volume histograms. *Int J Radiat Oncol Biol Phys* 1998, **41**(1), 83–92 issn: 0360-3016.

81 Jackson A, Skwarchuk MW, Zelefsky MJ, *et al*. Late rectal bleeding after conformal radiotherapy of prostate cancer. II. Volume effects and dose-volume histograms. *Int J Radiat Oncol Biol Phys* 2001, **49**(3), 685–98.

82 Wachter S, Gerstner N, Goldner G, Potzi R, Wambersie A, Potter R. Rectal sequelae after conformal radiotherapy of prostate cancer: dose-volume histograms as predictive factors. *Radiother Oncol* 2001, **59**(1), 65–70.

83 Marks LB, Carroll PR, Dugan TC, Anscher MS. The response of the urinary bladder, urethra, and ureter to radiation and chemotherapy. *Int J Radiat Oncol Biol Phys* 1995, **31**(5), 1257–80.

84 Emami B, Lyman J, Brown A, *et al*. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991, **21**(1), 109–22.

85 Blasko JC, Wallner K, Grimm PD, Ragde H. Prostate specific antigen based disease control following ultrasound guided ^{125}iodine implantation for stage T1/T2 prostatic carcinoma. *J Urol* 1995, **154**(3), 1096–1099.

86 Ragde H, Elgamal AA, Snow PB, *et al*. Ten-year disease free survival after transperineal sonography-guided iodine-125 brachytherapy with or without 45-gray external beam irradiation in the treatment of patients with clinically localized, low to high Gleason grade prostate carcinoma. *Cancer* 1998, **83**(5), 989–1001.

87 Ragde H, Korb LJ, Elgamal AA, Grado GL, Nadir BS. Modern prostate brachytherapy. Prostate specific antigen results in 219 patients with up to 12 years of observed follow-up. *Cancer* 2000, **89**(1), 135–41.

88 Stone NN, Stock RG. Prostate brachytherapy: treatment strategies. *J Urol* 1999, Aug(162).

89 Stock RG, Cahlon O, Cesaretti JA, Kollmeier MA, Stone NN. Combined modality treatment in the management of high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2004, **59**(5), 1352–9.

90 Critz FA, Levinson K. 10-year disease-free survival rates after simultaneous irradiation for prostate cancer with a focus on calculation methodology. *J Urol* 2004, **172**(6Pt1), 2232–8.

91 Duchesne GM. Radiation for prostate cancer. *Lancet Oncol* 2001, **2**(2), 73–81.

92 Singh AM, Gagnon G, Collins B, *et al*. Combined external beam radiotherapy and Pd-103 brachytherapy boost improves biochemical failure free survival in patients with clinically localized prostate cancer: results of a matched pair analysis. *Prostate* 2005, **62**(1), 54–60.

93 Sarosdy MF. Urinary and rectal complications of contemporary permanent transperineal brachytherapy for prostate carcinoma with or without external beam radiation therapy. *Cancer* 2004, **101**(4), 754–60.

94 Astrom L, Pedersen D, Mercke C, Holmang S, Johansson KA. Long-term outcome of high dose rate brachytherapy in radiotherapy of localised prostate cancer. *Radiother Oncol* 2005, **74**(2), 157–61.

95 Galalae RM, Martinez A, Mate T, *et al*. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004, **58**(4), 1048–55.

96 Martinez A, Gonzalez J, Spencer W, *et al*. Conformal high dose rate brachytherapy improves biochemical control and cause specific survival in patients with prostate cancer and poor prognostic factors. *J Urol* 2003, **169**(3), 974–9, discussion 979–80.

97 Pellizzon AC, Nadalin W, Salvajoli JV, *et al*. Results of high dose rate after loading brachytherapy boost to conventional

external beam radiation therapy for initial and locally advanced prostate cancer. *Radiother Oncol* 2003, **66**(2), 167–72.

98 Hoskin PJ. High dose rate brachytherapy boost treatment in radical radiotherapy for prostate cancer. *Radiother Oncol* 2000, **57**(3), 285–8.

99 Bolla M, Gonzales 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**(5), 295–300.

100 Shahidi M, Norman AR, Gadd J, Huddart RA, Horwich A, Dearnaley DP. Recovery of serum testosterone, LH and FSH levels following neoadjuvant hormone cytoreduction and radical radiotherapy in localised prostate cancer. *Clin Oncol* 2001, **13**(4), 291–295.

101 Parker C, Dearnaley D. Re: All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst* 2002, **94**(11), 861–2; discussion 865–6.

102 Kirk D. Re: A structured debate: immediate versus deferred androgen suppression in prostate cancer – evidence for deferred treatment. *J Urol* 2002, **167**(2Pt1), 652, author reply 653.

103 Simon D, Charles MA, Nahoul K, *et al*. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. *J Clin Endocrinol Metab* 1997, **82**(2), 682–5.

104 Smith JC, Bennett S, Evans LM, Kynaston HG, Parmar M, Mason MD, *et al*. The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. *J Clin Endocrinol Metab* 2001, **86**(9), 4261–7.

105 Pilepich MV, Winter K, Lawton CA, *et al*. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma–long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005, **61**(5), 1285–90.

106 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 unfavorable prognosis carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001, **49**(4), 937–46.