Radiotherapy and hormonal treatment

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Introduction

Combined modality therapy has developed as the standard of care for the majority of cancers using combinations of chemoradiation as either non-surgical radical options as, for example, in cancers from head and neck, lung, cervix and oesophagus or in combination with surgery, as in breast cancer. In prostate cancer, hormonal therapy is the appropriate and most effective systemic treatment option. Phase III randomised trials have unequivocally demonstrated the benefits of both neoadjuvant androgen suppression with external beam radiotherapy in patients with intermediate and high risk localised disease [1] and for adjuvant therapy in men presenting with advanced stage, high grade (Gleason sum $\geqslant$8) disease [2–9]. Escalating radiotherapy dose has also been shown to improve outcome in men with localised prostate cancer [10–15] and the addition of pelvis to prostate alone radiotherapy improves outcome in men with a high risk of pelvic lymph node involvement [16]. Presently, there remains debate concerning the balance between neoadjuvant androgen suppression and dose escalation for patients with intermediate risk disease and of the duration of hormonal therapy for those men with more advanced presentations. There is evidence to suggest that both dose escalation and more prolonged duration of hormonal therapy may adversely affect outcome [17] and refinement of treatment to match patients' individual presenting characteristics remains a challenge. This chapter will review the available data and give the rationale behind current treatment approaches.

Classification of localised prostate cancer

Localised prostate cancer has been stratified into a variety of risk groups by different authors using combinations of clinical tumour and lymph node staging, histopathology using the Gleason grading system and the presenting prostate specific antigen (PSA) level [18–21]. All of these definitions have clinical utility, for example, in a multi-institutional pooled analysis of radiotherapy results, Shipley and colleagues showed that in a series of men treated to a mean dose of 69 Gy, the 5 year PSA control rates were 81%, 68%, 51% and 31% for men with initial presenting PSA levels of <10, 10–20, 20-<30 and $\geqslant$30 ngs/ml, respectively. This simple stratification closely approximated to a more complicated model based on logistic regression following multivariate analysis including presenting tumour stage and grade. A current consensus definition of risk groups is given in Table 1 [1] and this stratification is used in this chapter. However, it must be appreciated that patients entered into the various phase III trials described, have not been sub-categorised in this fashion and, additionally, with the passage of time, there has been both stage and grade 'migration' with the increasing use of PSA testing for early recognition of disease and changes in the appreciation of Gleason grading [22].

Table 1
National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [1]

Low Risk	T1-T2a and Gleason Score 2–6 and PSA <10 ng/ml
Intermediate Risk[a]	T2b-T2c or Gleason Score 7 or PSA 10–20 ng/ml
High Risk[a]	T3a or Gleason Score 8–10 or PSA >20 ng/ml
Very High Risk	T3b-T4 or N1

[a] Patients with multiple adverse factors may be shifted into the next higher risk group.

The combination of hormonal treatment with external beam radiotherapy

The potential advantages of combined modality treatment using androgen suppression and external beam radiotherapy include (i) an additive or synergistic effect on tumour cell kill; (ii) a reduction in radiation target volume and (iii) reduction in the development of metastases from 'spatial co-operation'. The first mechanism would have potential benefit by improving local control of disease and potentially by decreasing local disease persistence or recurrence reducing a 'second wave' of metastases. This type of benefit might be expected to occur after quite prolonged patient follow-up. The second mechanism might favourably reduce the radiation target volume and, therefore, potentially reduce treatment related side effects. The third mechanism of 'spatial co-operation' describes the typical benefit of successful adjuvant therapy – for example, Tamoxifen in breast cancer, whereby disease recurrence and development of metastases is delayed and reduced, improving subsequent overall survival presumably by eradicating sub-clinical micrometastases present at the time of initial therapy. All of these mechanisms may have a role in prostate cancer management.

Hormonal treatment and volume reduction

Several groups, including our own, have measured the reduction in prostate and prostate radiotherapy target volume after initial hormone treatment. Prostate volume reduction has been shown to vary between 25% and 41% in the different studies [23–25]. It has also been demonstrated that there is a complementary decrease in the volume of rectum and bladder treated following initial hormone treatment. The variability between the different series most probably relates to varying amounts of prostate cancer bulk prior to initiation of hormone therapy. Only one study has attempted to measure subsequent clinical benefit. In a small (125 men) randomised pilot study of dose escalation, there was a second randomisation of the radiotherapy margin to be placed around the prostate of either 1.0 cm or 1.5 cm. The 5 mm reduction in margin approximated to the average reduction in diameter of the prostate after 3–6 months of initial androgen suppression. The results showed no difference in tumour control but a significant reduction in rectal side effects using the 1.0 cm margin (RTOG $\geqslant$ Grade 2 toxicity 21% versus 13%, $P = 0.005$) [11]. Our group has, therefore, recommended that the smaller margin matching the prostate volume after initial hormone therapy should be used in the radiotherapy planning process.

Effect of combined modality hormone therapy and radiation on disease control

The first convincing demonstration of an overall survival benefit for combined modality therapy was shown in EORTC trial 22863 by Bolla and colleagues in 1997 [26]. This trial used 3 years of androgen suppression and since then our understanding of the appropriate use of hormone therapy and adjuvant radiotherapy has been informed by the results of several important randomised trials using both short course neoadjuvant (approximately 6 months) or longer ($\geqslant$2 years) of adjuvant androgen suppression.

Short course or neoadjuvant androgen suppression

Four research groups have reported results from randomised controlled trials comparing short course (4–6 months) androgen suppression combined with radiotherapy compared with external beam radiotherapy alone (Table 2). The first such study, RTOG 86–10, randomised 470 men with bulky T2-T4 cancers to receive either radiotherapy alone or radiotherapy and 4 months of androgen suppression, 2 months before and 2 months during radiotherapy. Men with lymph node involvement were eligible. The radiotherapy was given to either the prostate alone (65–70 Gy) or with an additional pelvic field (dose 44–46 Gy) [8]. After a median follow up of 8.7 years there was a non-significant trend towards improved overall survival for the group receiving both irradiation and hormone therapy (8 years' survival: 53% versus 44%, $P = 0.10$). However, a statistically significant survival advantage was seen in the sub-group of 129 men with Gleason 2–6 disease in whom 8 year overall survival was 70% for combined treatment compared to 52% for radiotherapy alone ($P = 0.015$). More recently, a set of Canadian trials including a total of 481 men with T2-T3 disease used either a 5 month or 10 month course of androgen suppression which commenced 3 months prior to radiotherapy compared to radiotherapy alone. After a 5 year median follow-up the 7 year biochemical failure free survival was 66% in the combined modality group, using 5 months of hormonal treatment compared to 42% with radiotherapy alone ($P < 0.01$). There was no advantage for the longer 10 month course of treatment (PSA control at 7 years 69%, $P = 0.6$) compared to the 5 month course of androgen suppression. In

Table 2
Conformal radiotherapy with or without 3–6 months androgen suppression

Trial/Author	End point	RT	RT + LHRHa	P
Quebec Laverdiere 2004 [7]	7 y PSA failure free survival	42%	66%	$P \leqslant 0.01$
TROG 96–01 Denham 2005 [4]	5 y PSA failure free survival	38%	52/56%	$P \leqslant 0.002$
Boston D'Amico 2004 [3]	5 y survival free of salvage	57%	82%	P = 0.002
TROG 96–01 Denham 2005 [4]	5 y survival free of salvage	63%	68/78%	$P < 0.03$
RTOG 86–10 Pilepich 2001 [8]	8 y cause specific survival	69%	77%	P = 0.05
TROG 96–01 Denham 2005 [4]	5 y cause specific survival	91%	92/94%	P = 0.04 (6m)
Boston D'Amico 2004 [3]	5 y overall survival	78%	88%	P = 0.04
RTOG 86–10 Pilepich 2001 [8]	8 y overall survival	44%	53%	P = 0.1

a study performed in Boston [3] 206 men with intermediate or high risk localised prostate cancer (PSA $\geqslant$10 ngs/ml, Gleason score $\geqslant$7 or radiographic evidence of extra prostatic disease) were treated with radiotherapy to a dose of 70 Gy to the prostate region only and randomised to either no hormonal treatment or 6 months of androgen suppressive therapy. After a median follow-up of 4.5 years, patients randomised to receive radiotherapy and androgen suppression had a significantly higher 5 year overall survival (88% versus 78%, P = 0.04), lower prostate cancer specific mortality and higher survival free of salvage hormonal treatment (82% versus 57%, P = 0.002). In this study, the androgen suppression commenced 2 months prior to radiotherapy. The largest study has been performed by the Trans-Tasman Radiotherapy Oncology Group (TROG) [4]. In this study, which included 818 men with locally advanced prostate cancer (T2b–T4 N0, median PSA 14.4–16.4 μg/l), 16% of men had intermediate risk disease and 84% high risk disease. Patients were treated to a dose of 66 Gy to the prostate area alone and randomised amongst three groups which compared 0 months, 3 months and 6 months of androgen deprivation therapy starting, respectively, 3 and 5 months before irradiation. Those men assigned to the 3 months androgen suppression had significantly improved local failure free survival (hazard ratio 0.56, $P = 0.001$), biochemical failure free survival (hazard ratio 0.70, $P = 0.002$), disease free survival (hazard ratio 0.65, $P = 0.0001$), and freedom from salvage treatment (hazard ratio 0.73, P = 0.025) compared to the group having no androgen suppression. Those patients randomised to 6 months androgen suppression had additional improvements in improved local failure (hazard ratio 0.42, $P < 0.0001$), biochemical failure free survival (hazard ratio 0.58, $P \leqslant 0.0001$), disease free survival (hazard ratio 0.56, $P < 0.0001$), freedom from salvage treatment (hazard ratio 0.53, $P < 0.0001$), but also distant failure (hazard ratio 0.67, P = 0.046) and prostate cancer specific survival (hazard ratio 0.56, $P = 0.04$) compared with no androgen deprivation. There are theoretical reasons to believe that commencing androgen suppression prior to radiotherapy may be more beneficial than starting during or after treatment. Optimal timing of short course hormonal therapy was studied in RTOG trial 94–13 [16]. This trial with 1323 men who had an estimated risk of lymph node involvement of $\geqslant$15% were randomised to 4 months androgen suppression either before and during or alternatively after radiotherapy. After a median follow-up of 60 months there was a progression free survival advantage for men treated with whole pelvic radiotherapy and neoadjuvant androgen deprivation compared to those receiving whole pelvic radiotherapy and adjuvant treatment (PSA control at 4 years was 60% compared to 40% (hazard ratio 1.32, 95% confidence intervals 1.03 to 1.68)). The acceptability of short term androgen suppression has been assessed in the TROG trial [4]. It was found that maximal androgen blockade improved urinary symptoms prior to radiotherapy compared to the radiotherapy alone group and that sexual functioning was similar in all three randomised groups, one year after treatment. We have found that androgen levels are expected to recover in almost all men 6–12 months after 6 months or less hormone therapy provided that 1 month (rather 3 month) depot injections of LHRH analogue are used [27,28]. We have also shown that there is no long term detriment to testosterone levels, hormone levels being maintained 5 years after combined modality therapy [29]. It is noteworthy that relatively small numbers of men with good risk presenting features have been included in trials assessing short course hormonal therapy in combination with radiotherapy. EORTC trial 22991 [30] is randomising groups of patients with predominantly good or intermediate risk disease between high dose conformal radiotherapy alone and CFRT with 6 months of androgen suppression using

Table 3
Short versus intermediate/long course androgen suppression with RT

	RTOG 92–02 [6]	Canadian [31]	Quebec [7]	TROG 96–01 [4]	RT0G 99–10	EORTC 22961	TROG: RADAR
No.	1554	378	296	818	1540	966	1000
PSA	20	10	12	15	–	–	–
Stage	T2–T4	T1c–T4	T2–T3	T2–T4	Intermediate and high risk	Intermediate-very high risk	Intermediate-high risk
Hormone Duration	4m–28m	3m–8m	5m–10m	3m–6m	4m–8.5m	6m–36m	6m–18m
RT prostate/pelvis (Gy)	65–70/45	66/45	64/–	66/–	–	–	Centre dependent
Status	Reported	Reported	Reported	Reported	Completed	Completed	Ongoing

two 3-month depot LHRH analogue treatments. A total of 800 patients will be randomised.

Short versus long course androgen suppression

The duration of androgen suppression is important not only because of the prolonged andropausal side effects that will accompany longer courses of androgen suppression but also because there may be an increased risk of cardiovascular disease, diabetes and osteoporosis. A total of seven randomised controlled trials have been designed to address this issue (Table 3), four of these have compared short durations of hormonal treatment (3–5 months versus 6–10 months), two short duration versus long duration (4–6 months versus 28–36 months) and one short course versus intermediate duration (6 months versus 18 months). Six of the seven trials have completed recruitment and four have been reported. Of these, three have reported differing durations of relatively short course treatment (Table 3 [4,7,31]). Overall, the two Canadian trials [7,31] did not show advantages for the longer courses of hormone treatment (8–10 months) compared to shorter (3–5 months). These studies were undertaken in patients with relatively good presenting features as can be judged by the median PSA levels of 10 and 12 respectively. The TROG 96–01 mentioned above recruited patients with more adverse presentations (median PSA 15) and suggested that the 6 month hormonal schedule was more beneficial than the 3 months having an impact on metastasis free survival. It may be relevant that the Canadian study suggested a benefit for the longer course of hormonal treatment for high risk patients only [31]. The largest study reported to date is RTOG 92–02 in which 1554 men with locally advanced disease (T2c-T4) received radical radiotherapy with 4 months of neoadjuvant maximal androgen blockade and were randomly allocated to an additional 2 years adjuvant Goserelin or observation [6]. Overall, the duration of adjuvant hormone therapy had no effect on survival. Five year overall survival was 78% versus 79% for long and short term adjuvant therapy respectively. However, sub group analysis of patients with Gleason 8–10 disease demonstrated a significant survival advantage for long term therapy with 5 year survival of 80% versus 69% ($P = 0.02$). Although there is a significant downside in terms of extra morbidity to the use of long term (rather than short term) adjuvant hormone therapy, the absolute survival benefit of approximately 10% at 5 years for this subgroup will, for most men, outweigh the detrimental effects on quality of life. We have looked at the data from this trial for men with Gleason $\leqslant 7$ [17]. 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 a suggestion 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%). It is well documented that androgen suppression can cause increases in body mass index, increased arterial stiffness, unfavourable lipid profiles as well as anaemia and osteoporosis [32–36]. A recent large review from the Surveillance, Epidemiology and End Results (SEER) and Medicare databases showed an association of new diagnoses of fatal and non-fatal cardiac disease and diabetes with androgen suppression [37]. Similarly, a recent preliminary report using data from the CaPSURE database compared men who had been treated with radiotherapy with varying durations of hormone therapy and the analysis suggested that the duration of hormone treatment was associated with a shorter time to all cause mortality. The increase in cardiovascular mortality associated

Table 4
Radiotherapy alone or with long term androgen suppression

	EORTC 22863 [2] 5 yr actuarial results	RTOG 85–31 [8]10 yr actuarial results	Swedish Trial [5] 9 yr crude results
Freedom from local recurrence	84% versus 98% ($P \leqslant 0.0001$)	61% versus 77% ($P \leqslant 0.0001$)	
Freedom from distant metastases	71% versus 90% ($P \leqslant 0.0001$)	61% versus 75% ($P \leqslant 0.0001$)	
Freedom from PSA failure	45% versus 76% ($P \leqslant 0.0001$)	9% versus 30% ($P \leqslant 0.0001$)	
Clinical progression free survival	40% versus 74% ($P \leqslant 0.0001$)		56% versus 73% ($P = 0.06$)
Cause specific survival	79% versus 94% ($P \leqslant 0.0001$)	78% versus 83% ($P \geqslant 0.005$)	71% versus 90% ($P = 0.02$)
Overall survival	62% versus 78% ($P \leqslant 0.0001$)	38% versus 53% ($P = 0.0004$)	39% versus 69% ($P = 0.005$)

with androgen suppression was significant in men over but not under 65 years of age [38]. A recent analysis of 311 men of median age 70 who were enrolled in three of the randomised controlled trials [2–4] has additionally suggested that, adjusting for other known prognostic factors, the treatment of node negative high risk prostate cancer patients using 3 years as compared to 6 months of androgen deprivation was not associated with prolonged survival [39]. This emphasises the importance of not accepting long term androgen suppression as the standard of care unless men have particular adverse features (Gleason score $\geqslant 8$ and T stage $\geqslant 3$) at presentation. In view of the potential adverse effects of hormonal therapy, it also follows that future clinical trials for adjuvant therapy should use overall and not disease specific survival as the main end point.

Long course androgen suppression

The EORTC trial 22863 results initially reported in 1997 were updated in 2002 [26]. This trial randomised 405 men with T3-T4 cancers and/or high grade prostate cancer to receive either pelvis and prostate radiotherapy alone or radiotherapy plus concurrent and adjuvant Goserelin for 3 years. There was a marked and statistically significant improvement in overall 5 year survival in the combined modality treatment group with survival of 79% (confidence intervals 72–86%) compared with the radiotherapy alone group out of survival 62% (confidence intervals 52–72%). In North America, the RTOG 85–31 trial recruited 977 men with T3 and/or N1 disease. Randomisation was between radiotherapy alone or radiotherapy and the addition of long term adjuvant hormonal therapy which started at the end rather than the beginning of radiotherapy as in the EORTC trial. Initial results showed an overall survival advantage only in the subgroup of patients with Gleason 8–10 cancers but updated results show this effect extends to the entire study population with a 10 year actuarial survival rate of 53% for the combined modality group compared to 38% for the radiotherapy alone group [9,40]. A similar benefit was seen in a small Swedish trial which randomised men with pathological lymph node involvement to receive radiotherapy with or without orchidectomy. Those treated with castration had an overall improvement in survival to 69% compared to 39% at 9 years (Table 4). It must be appreciated that these three important studies recruited and randomised men approximately 20 years ago and presentations with such advanced localised disease are considerably less common than in the past. Nevertheless, it is quite clear that long term androgen suppression offers clinically significant advantages for patients with locally advanced and high grade or node positive cancers not only in terms of biochemical control of disease but also freedom from distant metastases as well as cause specific and overall survival. A major, current challenge is to separate patients into those groups who should receive shorter rather than longer course hormonal treatment. Further randomised trials are addressing this issue. RTOG 99–10 has recruited 1540 men with intermediate or high risk localised disease and has compared 4 versus 8 months of total androgen suppression prior to and during radiotherapy. EORTC trial 22961 has compared 6 months with 36 months of androgen suppression in addition to prostate and pelvis radiotherapy; preliminary results are expected shortly. RTOG 99–02 has recruited 1,440 high risk patients comparing initial and adjuvant hormonal therapy with irradiation – and similar treatment but with the addition of four cycles of chemotherapy using paclitaxel, estramustine and itoposide. A recent report documents greater toxicity with the triple modality approach [41]. Whilst it is possible that such aggressive combined modality schedules may benefit younger men with prostate cancer, it should be appreciated that for more elderly men,

Table 5
Phase III randomised controlled trials of dose escalation in prostate cancer

Trial	No.	Status	Dose (Gy)	Initial PSA (ng/ml Mean)	Recurrence free survival % (lower vs. higher dose)	Hazard ratio	Late toxicity RTOG ⩾2 (%)	
							Bowel (lower vs. higher dose)	Bladder (lower vs. higher dose)
MDACC – 9301 [10]	305	Reported	70 vs. 78	8	64 vs. 70	0.56	8 vs. 17[b]	10 vs. 10
ICR/RMT Pilot [11]	126	Reported	64 vs. 74[a]	14	59 vs. 71	0.64	11 vs. 23[b]	11 vs. 18
PROG 95–09 [12]	393	Reported	70.2 vs. 79.2	6	60 vs. 80	0.43	12 vs. 26[b]	18 vs. 20
NKI CTO 96–10 [13,14]	669	Reported	68 vs. 78	15	54 vs. 64	0.77	27 vs. 32	39 vs. 41
MRC RT01 [15]	843	Reported	64 vs. 74[a]	15	60 vs. 71	0.67	24 vs. 33[b]	8 vs. 11
GETUG - 06	300	Completed	70 vs. 78					
RTOG 01–26	1520	In progress	72 vs. 78					

[a] 3–6 month neoadjuvant androgen suppress. [b] All $P \leqslant 0.02$.

androgen suppression alone may remain the treatment of choice.

An alternative hormonal management approach is to use an anti-androgen to block the action of testosterone rather than produce castrate levels using an LHRH analogue. Bicalutamide has been extensively studied in the early prostate cancer programme (EPC) [42–44], but no direct comparison has been made with an LHRHa in men treated with radiotherapy for localised disease. A total of 1370 men with T1-T4 N0 cancers were randomised to be treated with radiotherapy alone or the addition of Bicalutamide 150 mg given for 5 years. In the most recent update [43] after a median follow up of 7.2 years, there were advantages seen for the sub group of 305 men with locally advanced disease in progression free (hazard ratio 0.56, $P < 0.001$) and overall survival (hazard ratio 0.65, $P = 0.03$) with fewer prostate cancer deaths (16% Bicalutamide versus 24% control). However, there were no advantages seen for either progression free or overall survival in the 1065 men with 'localised' disease. This results are reminiscent of those described above in the RTOG 92–02 trial [6]. There is no information on the use of shorter courses of Bicalutamide in good or intermediate risk patients and further studies of the efficacy and side effects of Bicalutamide in comparison with an LHRHa are desirable.

Escalation of radiotherapy dose in the treatment of prostate cancer

Considerable advances in radiation technology over the last decade have led to the development of conformal radiation treatments which more closely match the high dose volume to the tumour target whilst reducing the radiation to dose limiting normal tissues [45]. The potential advantages of these techniques is to enable a reduction in radiation related side effects as well as permitting the safe delivery of high doses of radiation which might improve treatment efficacy. Institutional experiences and results from phase I/II studies suggest that both these goals may be achievable [46–48] and that dose/response relationships exist for tumour control as well as dose/volume relationships for the development of late normal tissue damage.

In a phase III randomised trial [49] we compared conventional and conformal radiotherapy (CFRT) at a standard dose of 64 Gy and showed a significant reduction in the dose limiting late side effect of proctitis using CFRT but no detriment in disease control. Four phase III trials (Table 5) using conformal photon beam treatment have reported gains in PSA control of between 6% and 12% using higher doses of radiation [10,11,14,15]. In the MD Anderson trial (MCACC 93–001), which compared 70 and 78 Gy, benefit (19% PSA control advantage) was restricted to men with a presenting PSA >10 ng/ml [10]. In the recently reported Dutch multicentre trial (CKTO 96–10) in which 664 men were randomised to receive treatment with 78 Gy or 68 Gy, there was a 10% PSA control advantage for the higher dose, which was most clearly seen in men with intermediate and high risk disease. A pilot study in 126 men performed by the Institute of Cancer Research and Royal Marsden Hospital showed a 12% overall control advantage. This study was adopted and developed into the Medical Research Council (MRC) RT01 trial which is the largest study to report to date including a total of 843 men. An 11% overall advantage in PSA progression free survival (71% versus 60%) was shown for the dose escalated group. This trial also

demonstrated that neoadjuvant androgen deprivation does not replace the need for dose escalation; the effects may be complementary as control rates appear superior to those using dose escalation alone in the other trials [15]. PSA control advantage was seen in all risk groups as in the PROG study (see below) but in contra-distinction to the MD Anderson and NKI studies. The MRC RT01 trial also suggested benefit in terms of clinical disease free survival and reduction in the need for salvage hormone treatment. None of these studies is yet mature enough to determine whether or not there is a reduction in metastases free or overall survival. Preliminary results using a proton beam boost (PROG 95–09) comparing doses of 70.2 Gy equivalent and 79.2 Gy equivalent suggests an 18% PSA control advantage in both low and intermediate risk groups [12]. These results build on the improvements in PSA control rates that have been previously reported in phase II studies in larger groups of men [46–48,50,51]. For example, the Memorial Sloan Kettering Group have reported outcome from 1100 men comparing doses in the range of 64 to 70 Gy and 76 to 86 Gy [52]. Using clinical stage, histological grade and presenting PSA to define prognostic groups showed 5 year actuarial PSA control rates of 77% versus 90% ($P = 0.05$) for the most favourable group, 50% versus 70% ($P = 0.001$) for the intermediate group and 21% versus 47% ($P = 0.002$) for the unfavourable group treated to lower or higher doses respectively. A critical issue is whether or not PSA control will clearly relate to disease recurrence or to overall survival. A retrospective analysis from the Radiotherapy and Oncology Group (RTOG) suggests that dose escalation may indeed be related to improved survival. In their study, which included 1465 men treated in four protocols between 1975 and 1992, men with high grade cancers who received higher radiation doses ($\geqslant$66 Gy versus <66 Gy) had a 20% lower risk of death from prostate cancer and a 27% reduction in overall mortality. This benefit was not seen in men with well or moderately differentiated cancers [53].

Results using pelvic lymph node irradiation

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 [54]. 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 [55] and without evidence of benefit, many clinicians omitted whole pelvic irradiation in view of its high risk of complications. RTOG trial 94–13 [16] recruited 1323 patients who had an estimated risk of lymph node involvement of $\geqslant$15%. Patients were randomly assigned to whole pelvic radiotherapy or prostate only treatment with a second randomisation to 4 months neoadjuvant or adjuvant androgen suppression. After a 5 year follow up pelvic radiotherapy was associated with a 4 year progression free survival of 54% compared with 47% in patients treated with prostate only radiotherapy ($P = 0.02$). It is not yet certain that this progression free difference will translate into an overall survival benefit. A recent subset analysis demonstrated that radiotherapy field size had a major impact on progression free survival and that whole pelvis rather than 'mini pelvis' or prostate only was required to see the potential disease control benefit and the investigators recommended that comprehensive nodal treatment was used in patients with a risk of lymph node involvement of >15%. 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 [56]. It should be noted that whole pelvis radiotherapy has been given in the trials of adjuvant hormonal therapy described above. 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 micro metastases. 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 conventional radiotherapy to 18% using conformal techniques but only 5% reaches this dose level using IMRT [57]. 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 [58]. Further follow-up and studies will be required to confirm the low level of toxicity and potential benefit.

Radiobiology of prostate cancer and normal tissue: rationale for hypofractionation

Recently, there has been considerable discussion concerning the radiobiology of prostate cancer's response to irradiation [59–67]. In general, increased radiation fractionation provides an increasing therapeutic advantage between tumour control and late treatment related

side effects in that fractionation spares late responding normal tissues more than tumours because tumours normally respond as early responding tissue [68]. This sensitivity to change in fractionation is expressed mathematically in the linear-quadratic formalism and is quantified by the alpha-beta ratio [68]. In general, late responding normal tissues have a low alpha-beta ratio (usually taken as approximately 3 Gy) whereas early responding tissues responsible for acute radiation reactions and most cancers have a high alpha-beta ratio (usually 8–10 Gy). Fractionation spares tissues with a low alpha-beta ratio and radiotherapy schedules are designed so as to keep late radiation reactions at an acceptable level. For this reason, most cancers are treated with 1.8–2 Gy daily fractions over a period of 6–8 weeks. However, studies deriving the alpha-beta ratio for prostate cancer from low dose rate brachytherapy treatments have suggested the alpha-beta ratio is 1.5 Gy (95% confidence intervals 0.8–2.2 Gy) [69] and 1.49 Gy (95% confidence intervals 1.25–1.76) [60]. A further analysis using external beam radiotherapy with high dose brachytherapy estimated the alpha-beta ratio at 1.2 Gy (95% confidence intervals 0.03–4.1 Gy) [65]. The most comprehensive analysis using data from a total of 3756 patients who were treated with fraction sizes between 1.8 Gy and 2.86 Gy with total doses of 57.4 Gy to 77.4 Gy respectively suggested that the alpha-beta ratio for the end point of biochemical recurrence was 3.7 Gy [70]. The alpha-beta ratio for late reactions in normal tissues is usually taken as 3 Gy for skin, mucosa and bowel. However, human data is quite imprecise but a recent review suggests that the alpha-beta ratio for radiation induced proctitis may be relatively high at 5.4 Gy ($\pm$1.5 Gy) [71]. If these estimates are accurate, they would predict that hypofractionated schedules for prostate cancer should produce tumour control and late treatment related sequelae that are at least as good or better than those currently achieved with currently standard schedules using 1.8–2.0 Gy daily fractions. However, different assumptions in the models used for calculating the alpha-beta ratios can lead to estimates as high as 10 Gy [59] and values of 8.5 Gy and 15.5 Gy have recently been derived by incorporating hypoxia into the modelling process [66].

Clinically hypofractionated external beam radiotherapy has been used for many years in the UK for a variety of malignancies, predominantly as a result of limited resources. In the past, satisfactory results were claimed using a variety of hypofractionated treatment schedules for prostate cancer varying from 50 Gy in 20 fractions over 4 weeks [72], 50 Gy in 16 fractions over 21 days [73] and 36 Gy in six treatments over 5 weeks [74]. Many centres in the UK continue to use 4 week radiotherapy schedules using total doses of between 50 and 55 Gy. Contemporary reports of hypofractionated schedules are limited. A phase III trial in 936 men has compared 52.5 Gy in 20 fractions with 66 Gy in 33 fractions. Preliminary results appeared to show a 7% reduction in PSA control rate (49% versus 56%) in the 20 fraction arm with hazard ratio for failure (short to long) of 1.20 (95% CI 1.0 to 1.44). Late toxicity was similar in the two arms (Grade 3/4 = 3%) [75]. A second, small, randomised controlled trial including 120 men compared a dose of 64 Gy in 32 fractions with 55 Gy in 20 fractions. After median follow up of 44 months, 4 year PSA control rates were similar (86.2% versus 85.4% for hypo and standard fractionation respectively); there was a slight excess of rectal bleeding in the hypofractionated group [76]. 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 [77]. All of these studies are compatible with an α/β ratio for prostate cancer of $\leqslant$1.5–3.0 Gy [78]. Additionally, a preliminary report from the USA [79] suggested that a dose of 70 Gy in 2.5 Gy fractions was at least as effective as 78 Gy in 2 Gy fractions. Presently, there are no long-term data using higher dose hypofractionated radiotherapy. Phase I studies using 3 Gy fractions have recruited in Manchester (57 Gy, 60 Gy) [80], Toronto (up to 66 Gy) (personal communication) and Japan (69 Gy) [81].

If the radiobiological predictions of a low alpha-beta ratio for prostate cancer are correct, such shortened schedules may be associated with improvements in tumour control for a given level of radiation related side effects. If this is the case, then such schedules should become the standard approach to treatment as they would be more convenient for patients and make better use of radiotherapy resources. To date, no phase III study of dose escalated conformal or intensity modulated radiotherapy using hypofractionated schedules has been reported, but studies have commenced in the UK [82], The Netherlands, Scandinavia and North America.

Conclusion

Strategies of dose escalation, neoadjuvant and adjuvant combined modality therapy using androgen suppression with radiotherapy are improving the disease control for men with both early and locally advanced disease prostate cancer. Completed phase III studies have refined indications for selection of patients

Table 6
Management strategies using external beam radiotherapy and hormone treatment in localised prostate cancer [1]

Low Risk	Recommended dose $\geqslant$70 Gy, 35 fractions (Volume prostate $\pm$ seminal vesicles). Some evidence for improved PSA control with short course NAD and doses 74 $\rightarrow$ 78 Gy.
Intermediate Risk	Level 1 evidence for use of NAD. Level 1 evidence for high dose conformal radiotherapy. Recommendation: 74–78 Gy in 2 Gy fractions (Volume prostate + SV). Duration of NAD $\geqslant$3–6 months.
High Risk	(i) Gleason $\leqslant$7. As above with 6 months NAD. (ii) Gleason $\geqslant$8 and T3. Level 1 evidence for 3 years androgen suppression. Consider pelvic RT for all cases.
Very High Risk	Level 1 evidence for 3 years androgen suppression. Prostate dose $\geqslant$70 Gy with pelvic dose $\geqslant$44–46 y in 2 Gy fractions with 3 years androgen suppression.

for these different approaches (Table 6) and ongoing studies will improve patient selection. However, both androgen suppression and dose escalation are associated with increased levels of side effects and it is essential that improved radiotherapy techniques are developed and tested so as to minimise both early and late morbidity.

Conflict of interest statement

I confirm I have no conflicts of interest.

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