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TOPIC PAPER

Evolution of definitive external beam radiation therapy in the treatment of prostate cancer

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Abstract

Purpose Although the clinical significance of a diagnosis of prostate cancer for some men is debated, for many men it leads to significant morbidity and mortality. Radical treatment of clinically localized prostate cancer has been shown to improve survival in men with intermediate or high-risk disease. There is no high level evidence to support the superiority of radical prostatectomy, with or without adjuvant or salvage external beam radiotherapy in comparison to definitive radiotherapy with or without androgen deprivation, and the choice should be individualized. External beam radiation therapy practices are in constant evolution, and numerous strategies have been investigated to improve either efficacy or reduce toxicity, or both.

Methods Randomized controlled trials investigating strategies to improve efficacy, reduce toxicity, or both of external beam radiotherapy have been reviewed in men with prostate cancer without nodal or distant metastases. These strategies include the use of neo-adjuvant and adjuvant androgen deprivation, dose-escalation, hypofractionation, whole pelvic radiation therapy, incorporation of improved imaging, image- guided radiation therapy, and adjuvant systemic therapy. The evidence to date for these strategies is discussed, noting limitations in applying the results of reported trials to men treated in contemporary settings.

Results A number of strategies have shown improvements in biochemical control using external beam radiotherapy. To date, only with the use of androgen deprivation therapy has this translated into improvements in disease specific and overall survival. This may reflect the long natural history of prostate cancer and high incidence of competing risks. Technological advances have enabled dose escalation with reduced toxicity, of paramount importance given the long natural history.

Results The use of external beam radiation therapy in prostate cancer is evolving with numerous strategies incorporated to improve outcomes. The optimum dose and fractionation and use of androgen deprivation or systemic adjuvants for each man is unclear based on current evidence and prognostic and predictive parameters. Patient preferences play an important role in chosen therapy. It is hoped that future studies better capture all prostate cancer- and treatment- related morbidity to clarify the optimal therapy choices for each man with prostate cancer.

Keywords Prostate cancer · Radiation therapy · Dose escalation · Hypofractionation

Introduction

Conflicting results from large randomized trials of PSA screening for prostate cancer have led to significant debate, not only about the value of screening, but about the value of treatments aimed to cure the disease [5, 132]. It is a common disease, being the second most frequently diagnosed cancer in men globally, with well over 1.2 million diagnosed in 2018 [19]. There is, however, significant debate about the clinical relevance for men of a diagnosis of prostate cancer. While it is commonly said that more men may die with prostate cancer than of prostate cancer, it is a heterogeneous disease, behaving very differently in different men. For many men, it causes significant morbidity or death and it therefore remains an important cause of morbidity and mortality globally, being the fifth most common cause of cancer death in men [19].

Much research has aimed to identify, for men diagnosed with prostate cancer that is localized to the prostate and seminal vesicles, the parameters that may predict the likelihood

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of significant morbidity or mortality. The most widely used risk stratification, suggests division into low, intermediate and high-risk groups according to these tumor factors (Table 1) [34, 58, 139]. More recently recognition of heterogeneity in outcomes in men within these risk groups has lead to further stratification. High-risk disease has been divided into localized and locally advanced cohorts in the EUA risk grouping shown as in Table 1 [106]. The NCCN guidelines divide low, intermediate and high risks further into very low, low, favorable intermediate, unfavorable intermediate, high and very high risk groups [109]. Additional factors such as PSA kinetics or PNI help to predict outcome [11, 31, 33]. For each man, consideration of these factors, in addition to patient factors, including estimates of life expectancy and comorbidities, allows some estimation of the likelihood of morbidity or mortality from prostate cancer, from which a decision can be made about whether attempts at curative treatment are justified.

The optimal curative treatment of clinically localized prostate cancer is unclear. Acceptable options include radical prostatectomy, external beam radiotherapy, interstitial brachytherapy, androgen deprivation therapy, combinations of these modalities, and active surveillance or watchful waiting (observation with treatment only for symptoms) [106, 130]. Radical prostatectomy, external beam radiotherapy and brachytherapy, with or without androgen deprivation therapy, are the potentially curative modalities. The most effective modality in terms of cure has not been established. Several randomized trials have aimed to measure the efficacy and toxicity of the different modalities. The early SPCG-4 randomized trial comparing radical prostatectomy with watchful waiting showed a significant improvement in overall survival, disease-specific survival and metastasis-free survival with surgery, but was conducted in an era prior to the widespread use of PSA, and thus its applicability to contemporary population of men with prostate cancer was questioned [13]. The survival benefit was largely limited to those men under 65 years of age. The subsequent PIVOT trial, also comparing radical prostatectomy with observation, was conducted in the PSA era. Although no significant difference was found in overall or prostate cancer specific survival with surgery for the entire randomized cohort, there was a reduction in the risk of bone metastases, and subset analysis identified improvements in survival in men with PSA > 10 and intermediate and high risk tumors [146]. Although these trials did not assess the efficacy of radiotherapy, they provide evidence that radical treatment can lower the risk of death or of developing metastases, particularly in men with intermediate and higher risk prostate cancer.

The recently published ProTECT trial randomized men with clinically localized prostate cancer to radical prostatectomy, external beam radiotherapy or monitoring [50]. After a median follow-up of 10 years, the risk of dying from prostate cancer was very low in all groups. Radical treatment reduced the risk of clinical progression, largely because of a reduction in the risk of metastases. Participants had predominantly low-risk prostate cancer. The median PSA under 5 ng/mL, over three quarters had a Gleason score of 6, and over three quarters had T1C disease. While this study provides justification for active surveillance, the results cannot be extrapolated to higher risk disease.

At the other end of the spectrum, locally advanced disease, defined variably although commonly accepted to describe cancer that has spread beyond the prostate capsule in the absence of clinically evident regional or distant spread, traditionally has been considered unsuitable for radical prostatectomy. Two randomized trials, outlined in Table 2 have shown a survival benefit with the addition of external beam radiation therapy to androgen deprivation compared with androgen deprivation alone [96, 143]. Both trials concluded that the combination of external beam radiotherapy and androgen deprivation should be the standard of care for locally advanced disease.

We therefore have evidence that for low-risk disease, radical treatment including RP and RT do not improve survival or reduce the risk of dying from prostate cancer compared with active surveillance. For locally advanced disease, RT improves prostate cancer specific and overall survival compared with ADT alone. For intermediate and high-risk clinically localized disease, PIVOT provides some evidence to support curative treatment, but for these men high quality randomized comparisons between surgery and radiotherapy

Table 1 Risk stratification according to T stage, PSA (ng/mL), Gleason score (GS) and N stage

	Low risk	Intermediate risk	High risk
D'Amico—all N0 (D'Amico et al. [34]	T1–2a PSA < 10 GS ≤ 6	T2b PSA > 10–20 GS 7	≥ T2c PSA > 20 GS 8–10
EUA [106]	T1–2a PSA < 10 GS ≤ 6 N0	T2b PSA > 10–20 GS 7 N0	Localized: T2c, PSA > 20 or GS 8–10, N0 Locally advanced: T3–4 or cN+, any PSA or GS

Table 2 Trials of androgen deprivation therapy (ADT) ± radiation therapy (RT)

	Participants	Control	Experimental	Median follow-up	Results
NCIC CTG PR.3/MRC UK PR07 [96]	Locally advanced (T3–4) or organ confined T2 with PSA > 40 or PSA 20–40 and GS ≥ 8 $n = 1205$	Lifelong ADT (LHRH agonist or orchiectomy, 2 weeks initial antiandrogen)	Lifelong ADT + EBRT: 4 field box 45 Gy/25 whole pelvis, prostate, SV, with prostate boost to 65–69 Gy or 65–69 Gy prostate alone	8 years	Overall survival improved with RT; HR 0.7 (95% CI 0.57–0.85; $P < 0.001$) Prostate cancer death reduced; HR 0.46 (95% CI 0.34–0.61; $P < 0.001$) Higher frequency bowel toxicity with RT, but only 2 men ≥ G2 bowel toxicity at 24 months
SPCG-7/SFUO-3 (Widmark et al. [143]	T1b–2 WHO G2–3 or T3 (~ 78%) PSA < 70 ng/mL	Total androgen blockade: LHRH agonist 3 months + flutamide until progression or death	Same total androgen blockade + EBRT: 3D conformal RT 50 Gy to prostate/SV + 20 Gy boost to prostate 20 mm field margin	7.6 years	Overall survival improved with RT; HR 0.68 (95% CI 0.52–0.89; $P = 0.004$) Prostate cancer death reduced; HR 0.44 (95% CI 0.30–0.66; $P < 0.0001$) Higher frequency of urethral stricture, urinary urgency, incontinence and erectile dysfunction

are lacking. A number of non-randomized comparisons of surgery with external beam radiotherapy and brachytherapy have been published, and have suggested superior results for radical prostatectomy [25, 77, 134, 149]. Despite attempts to control for confounding variables, these cannot control for unknowns, including the absence of surgical staging of nodes in men receiving radiation therapy, and all comorbidities and competing risks.

Men who undergo radical prostatectomy who are found to have extracapsular extension, seminal vesicle invasion or positive surgical margins are at increased risk of recurrence, and post-operative radiotherapy has been used to reduce this risk. Three randomized trials to date have shown that adjuvant radiation therapy reduces the risk of biochemical failure [16, 140, 144]. Although the older SWOG 8794 trial found significant improvements in overall survival and metastasis-free survival, the more recent EORTC 22911 and ARO 96-02/AUO AP 09/95 trials did not, possibly reflecting effective salvage therapy for biochemical failure. There is no high-level evidence to support the superiority of a primarily surgical or radiation therapy approach. These modalities differ in the logistics of treatment, and their side effect profile, particularly if combined modality treatment is used, and both should be discussed. For each man, the choice will depend on personal consideration of relative benefits, logistics and potential side effects. Ideally treatment should be aimed at cure, with minimization of treatment related toxicity, and ideally with preservation of urinary continence and potency.

The different curative modalities cannot be compared on the basis of biochemical failure. The definition of biochemical failure definition differs following RP and RT, and 'failure' does not have the same implication in terms of subsequent risk of prostate cancer metastases or mortality. Traditionally, external beam radiotherapy trials have used the ASTRO definition of biochemical failure, defined as occurring after three consecutive rises in PSA after a nadir, with the date of failure being halfway between the nadir date and the first rise, or the initiation of salvage therapy [4]. This was of limited clinical relevance, correlating poorly with clinically relevant outcomes, largely due to backdating and sensitivity to the use of androgen deprivation. The RTOG-ASTRO Phoenix Consensus endorsed the adoption of the Phoenix definition of prostate cancer in 2005, defined by a rise of 2 ng/mL or more above the nadir PSA [127]. Although biochemical failure increases the risk of subsequent clinical failure, not all men who develop PSA failure will go on to develop metastases or die from prostate cancer, and there may be a significant lag between time PSA failure and metastases or death [27]. PSA is not a surrogate for prostate cancer death, and therefore, more clinically relevant outcomes are recommended [83]. As mentioned, given the variable and sometimes long natural history, long follow-up is necessary.

Although the more recently published trials have measured clinically relevant outcomes, including overall mortality, prostate cancer-specific mortality, metastasis-free survival, freedom from androgen deprivation, and comprehensive prospective assessment of toxicity and quality of life, there have been significant advances in both surgical techniques, and radiation therapy, which should be considered when applying the results of these studies to men

presenting today. The strategies that have been investigated to improve outcomes with definitive external beam radiotherapy are the focus of this review.

Many strategies have been explored to improve the outcome for men undergoing external beam radiotherapy, aimed both at improving efficacy and the chance of cure or long-term growth restraint, and reducing the risk and severity of side effects. These include:

1. Neoadjuvant and adjuvant androgen deprivation therapy (ADT).
2. Dose-escalated radiation therapy (DERT).
3. Increasing conformality.
   (a) CT planning—3D conformal radiotherapy (3DCRT).
   (b) Highly conformal techniques—IMRT, VMAT, HT.
4. Incorporation of image guidance radiation therapy (IGRT).
5. Rectal spacers.
6. Whole pelvic radiation therapy (WPRT).
7. Hypofractionation (HF).
8. Extreme hypofractionation—SBRT.
9. Incorporation of new imaging—MRI, PSMA.
10. Adjuvant systemic therapy.

Androgen deprivation

Prostate cancer cell growth androgen dependence has been recognized since the work of Huggins and Hodges in the early nineteenth century [65]. It has been an effective therapy for metastatic disease for many decades. Based on its efficacy in the metastatic setting, and high rates of recurrence in localized disease with radiotherapy alone, ADT has been investigated with radiotherapy for localized disease. Neoadjuvant androgen deprivation has the potential to cytoreduce disease prior to treatment, and potentially reduces the volume needed to be treated. Preclinical studies suggest that neoadjuvant therapy may increase radiosensitivity by impairment of DNA repair, reducing the dose required for sterilization [48, 72, 117, 153]. Androgen deprivation may also act on microscopic metastatic disease. Numerous randomized trials have investigated the use of androgen deprivation therapy (ADT) in combination with radiotherapy to improve the chance of cure, either neoadjuvantly, or adjuvantly, the features of which are outlined in Table 3. The majority of these trials have been performed with doses of radiation that would be considered relatively low by current standards. To date, ADT is the only strategy which has resulted in convincing improvements in overall and disease-specific survival, without increasing radiation related toxicity. It is, however, associated with well-recognized toxicity.

Four randomized trials have compared radiotherapy alone with the use of short term neoadjuvant and concomitant ADT, showing improvements in prostate cancer-specific survival or overall survival [32, 42, 68, 124]. Three randomized trials have attempted to clarify the optimal duration of neoadjuvant ADT [26, 42, 116]. In TROG 96.10, 6 months of ADT resulted in improved overall and disease-specific survival compared with no ADT, whereas 3 months did not significantly improve outcomes compared with radiotherapy alone. In the study by Crook and colleagues, an improvement with longer duration of neoadjuvant therapy was only apparent in the subset with Gleason score of 8 or more. No clear benefit was seen with 4 months compared with 9 months in RTOG 99.10.

Three trials with predominantly high-risk participants have compared radiotherapy alone with radiotherapy and adjuvant ADT: RTOG 85.31 (median 2.2 years), EORTC 22863 (3 years), and EORTC 22991 (6 months) [15, 17, 115]. Although short-term ADT did not result in improved survival in EORTC 22991, longer term ADT (2 or 3 years) resulted in clear improvements in overall in RTOG 85.31 and EORTC 22863, with absolute improvements in 10-year survival of 10% and 18%, respectively. Subset analysis within RTOG 85.31 suggested improvements in survival were confined to the subset with Gleason score 8–10 tumors.

Three trials have assessed the effect of long term ADT when neoadjuvant therapy is given: RTOG 9202, TROG RADAR and DART [41, 61, 69, 89, 148]. TROG RADAR found improved prostate cancer-specific survival, and RTOG and DART both found significant improvements in overall survival. Importantly, men in DART were treated with dose-escalated radiation therapy, with a median dose of 78 Gy used. Most of the preceding trials used relatively low radiotherapy doses, and the effect of androgen deprivation in the setting of dose escalation was unknown.

Together the above trials support the use of neoadjuvant androgen deprivation for intermediate risk disease, and the addition of long-term androgen deprivation for high risk disease. Importantly, however, intermediate risk encompasses a heterogeneous group, and ongoing trials will be needed to identify those men for whom androgen deprivation is unlikely to be of benefit and toxicity can be avoided, either using traditional or novel parameters such as molecular profiling.

The optimal duration of ADT in men with high-risk disease is debated. Two randomized trials have compared different durations of adjuvant therapy. EORTC 22961 compared 6 months with 3 years of adjuvant therapy, and found that 3 years improved survival, with 5-year survival 85% versus 81%, suggesting that 6 months was insufficient

Table 3 Androgen deprivation therapy (ADT)

Study	Participants	Control	Experimental	RT	Median F/U	Results
RTOG 8610 [124]	1987–1991 $n=456$ Bulky ≥ T2B; node +ve eligible if below common iliacs	RT alone	STAD 4 months, RT starting after 2 months	WPRT to 44–46 Gy in node –ve Boost to prostate 65–70 Gy		10-year OS 43% (ADT) vs 34% (HR 1.18 (95% CI 0.96–1.46); $P=0.2$ 10-year disease-specific survival: 23% (ADT) vs 36% $P=0.01$ 10-year distant metastases: 35% (ADT) vs 47% $P=0.006$
RTOG 94.08 [68]	1994–2001 $n=1979$ T1b–2bN0M0 with PSA ≤ 20 ng/mL	RT alone	STAD 4 months, RT starting after 2 months	WPRT 46.8 Gy Boost to prostate 19.8 Gy → 66.6 Gy (1.8 Gy/fraction)	9.1 years	No significant difference in overall survival (OS) 10-year disease-specific survival 8% vs 4% post hoc subset analysis suggested benefit in intermediate risk group; high risk numbers small
D'Amico et al. [31]	1995–2001 $n=206$ clinically localized prostate (low risk excluded) 58% GS 7 14% GS 8–10	RT alone	RT with 6 months ADT (2 months before, 2 months during and 2 months following) LHRH agonist + flutamide	3DCRT prostate/SV to 45 Gy in 25 Boost to prostate 22 Gy in 11 → ~ 70 Gy	4.5 years	Improved OS with ADT—5-year OS 88% (ADT) vs 78%
TROG 9601 [42]	1996–2000 $n=802$ ≥ T2b–4N0	(1) RT alone	(2) 3 months STAD–RT starting after 2 months (3) 6 months STAD–RT starting after 5 months goserelin + flutamide	66 Gy prostate/seminal vesicles; no pelvic node	10.6 years	3 month cf RT alone—no effect on distant progression (DP), prostate cancer specific mortality (PCSM) or overall mortality (OM) 6 month cf RT alone: improved DP: HR 0.49 (95% CI 0.31–0.76); $P=0.001$ PCSM: HR 0.49 (95% CI 0.32–0.74); $P=0.0008$ OM: HR 0.65 (95% CI 0.48–0.83); $P=0.0008$
Crook [26]	1995–2001 $n=378$ all T stages N0M0 low risk 29/22% intermediate 43/43% high risk 29/34%	3 months NADT goserelin + flutamide	8 months NADT goserelin + flutamide	Starting within 2 weeks completion NADT 3DCRT 4 or 6 field WPRT 45/46 Gy Boost to prostate 66/67 Gy	6.6 years	No difference in DFS Subset analysis—improvement in DFS with 8 months in high risk subset. No difference in low or intermediate risk

Table 3 (continued)

Study	Participants	Control	Experimental	RT	Median F/U	Results
RTOG 9910 [116]	2000–2004 $n=1579$ T1b–4 GS2–6, PSA > 10 ≤ 100 ng/mL or T1b–4 GS 7, PSA < 20 or T1b–c GS8–10, PSA < 20 10% GS 8–10; predominantly intermediate risk	4 months NADT (2 months before and 2 during RT) goserelin + bicalutamide or flutamide	9 months NADT (7 months before and 2 during)	2D or 3DCRT 70 Gy in 39 seminal vesicles, internal and external iliac nodes based on risk	9.4 years	No difference in disease-specific survival, metastasis-free survival, local recurrence or biochemical recurrence
RTOG 8531 [115]	1987–1992 $n=977$ Those not fitting size criteria RTOG 86.10, T3 (82%) or N1 (18%)	RT alone	RT with ADT indefinitely or until signs of progression, starting last week of RT goserelin Median duration 2.2 years	WPRT to 44–46 Gy Boost to prostate 20–25 Gy	7.6 years	ADT improved: 10-year OS: 39% (RT alone) vs 49% (ADT); $P=0.002$ 10-year DSS: 78% (RT alone) vs 84% (ADT) $P=0.005$ Subset analysis suggested OS benefit limited to GS7–10
EORTC 22863 [17]	1987–1995 $n=415$ T1–2 WHO G3 or T3–4 any grade (i.e. high risk)	RT alone	RT with 3 years of ADT goserelin starting with RT Cyproterone starting 1 week before goserelin, for 1 month	WPRT to 50 Gy Prostate/seminal vesicle boost of 20 Gy	9.1 years	ADT → increased overall survival: 10 years 39.8% vs 58.1% (HR 0.6 (95% CI 0.45–0.8), $P=0.0004$) Reduced prostate cancer mortality: 10-year PCM 30.4% vs 10.3% HR 0.38 (95% CI 0.24 5–0.6); $P<0.0001$) Increased clinical disease-free survival
EORTC 22991 [15]	2001–2008 n = 819 T1b–2aN0M0 PSA > 10, GS ≥ 7 or T2b–4 PSA up to 12.5 × ULN (~ 3/4 intermediate risk, ¼ high risk D'Amico)	RT alone	RT with 6 months ADT starting day 1 RT, LHRH agonist + anti-androgen 1 month	3DCRT or IMRT Prostate, seminal vesicle + WPRT if LN +ve risk > 15% (Roach) To 46 Gy Boost to prostate/SV to 70 Gy Optional boost 0,4 or 8 Gy (centers to specify for all)	7.2 years	Improved biochemical progression free survival and clinical progression free survival No OS difference

Table 3 (continued)

Study	Participants	Control	Experimental	RT	Median F/U	Results
RTOG 9202 (Lawton et al. [89]	1992–1995 $n=1554$ 'Locally advanced non-metastatic': cT2c–4N0/NX/M0 with PSA < 150 ng/mL	4 months NADT (2 months before and 2 months during RT) goserelin + flutamide	Same NADT, followed by 24 months of ADT goserelin alone (LTAD)	4 field WPRT 44–46 Gy Boost to prostate 65–70 Gy T2c, 67.5–70 Gy T3/4	19.6 years	LTAD: improved disease-free survival 29% relative reduction ($P<0.0001$); reduced local progression (46% relative risk reduction, $P=0.02$); reduced distant metastases (36% relative risk reduction, $P<0.0001$); improved disease-specific survival (30% relative reduction, $P=0.003$); improved overall survival (12% relative reduction, $P=0.03$)
TROG 0304 RADAR [69]	2003–2007 $n=1071$ T2a–4N0M0, PSA ≥ 10 ng/mL (GS ≥ 7 in T2a)	6 months NADT (before and during) leuprolide	Same 6 months NADT + further 12 months ADT	66, 70 or 74 Gy (centers to prespecify) or 46 Gy EBRT with HDR boost 19.5 Gy in 3 Further randomization ± Zometa 12 months	10.4 years	Reduction in prostate cancer-specific mortality with ADT: HR 0.7 (95% CI 0.5–0.97; $P=0.035$)
DART [148]	2005–2010 $n=255$ T1c–3bN0M0, intermediate (45%/48%) and high risk (55%/52%)	STAD: 4 months of neoadjuvant and concomitant ADT (2 months before and 2 during RT; goserelin and flutamide first 2 months)	LTAD: Same initial 4 months, followed by 24 months adjuvant goserelin	3DCRT to minimum 76 Gy (> 70% ≥ 78 Gy) WPRT permitted high risk (6% STAD/12% LTAD)	5.25	Increase in 5-year biochemical disease-free survival: HR 1.88 (95% CI 1.12–3.15; $P=0.001$) Increase in 5-year overall survival: HR 2.48 (95% CI 1.31–4.68; $P=0.009$) Increase in 5-year metastasis-free survival: HR 2.31 (95% CI 1.23–3.85; $P=0.01$) No increase in toxicity Subset analysis suggested benefit in high risk group; no significant effect in intermediate risk group with the current follow-up

Table 3 (continued)

Study	Participants	Control	Experimental	RT	Median F/U	Results
EORTC 22961 [14]	1997–2001 $n=970$ T1c–2a/b N1–2M0 or T2c–4 N0–2M0 (note > 90% N0, majority T2c–3)	6 months NADT (LHRH agonist + antiandrogen) alone (STAD)	Same NADT, followed by further 2.5 years ADT (LADT) LHRH agonist alone	3DCRT 3 or 4 field WP unless 'lymph nodes not invaded' to 50 Gy, boost to prostate/seminal vesicles to 70 Gy	6.4 years	OS inferior with STAD: 5-year overall survival 81% vs 85% ($P=0.02$) 5-year overall mortality 19% (STAD) vs 15% (LTAD) HR 1.42 (95% CI UL 1.79) Qol measures same No difference in cardiac events Increased gynecomastia, incontinence, sexual dysfunction LTAD
PCS IV [107]	2000–2008 $n=630$ High risk localized	4 months NADT (goserelin, bicalutamide 1 month) 36 months ADT	Same 4 months NADT 18 months ADT	3DCRT WPRT 44 Gy in 22 Boost to prostate/Sv 70 Gy in 35	9.4 years	No difference in overall survival 5-year OS 91% (36 m) versus 86% (18 m) $P=0.07$ (not powered for equivalence) QoL favored 18 m

STAD short term androgen deprivation, *WPRT* whole pelvic radiation therapy, *3DCRT* three-dimensional conformal radiation therapy, *NADT* neoadjuvant androgen deprivation therapy, *LN* lymph node, *LTAD* long-term androgen deprivation, *HDR* high dose rate brachytherapy, QoL quality of life

[14]. In contrast PCS IV, which compared 36 months with 18 months of ADT after 4 months of neoadjuvant therapy found no difference in overall survival. It was, however, a superiority trial, and therefore not powered to confidently exclude inferiority of a shorter course [107].

ADT is associated with well-recognized toxicities, including reduced libido and sexual dysfunction, vasomotor symptoms, fatigue, cognitive effects, emotional effects, gynecomastia, reduced penile and testicular size, hair loss and osteoporosis. More recently, a number of studies have found an increased risk of metabolic syndrome with ADT, with an increased risk of diabetes and cardiovascular disease including myocardial infarction, heart failure and arrhythmias, cerebrovascular disease and venous thromboembolism [9, 18, 30, 52, 73, 79]. Some studies have suggested that the risks are increased only in those with preexisting cardiovascular disease [108, 112, 151]. Other studies have not identified significant increases. This may reflect differing relative risks in different patient populations, particularly in lower prostate cancer risk groups for whom ADT confers minimal benefit in terms of reducing prostate cancer death. Nguyen and colleagues performed a meta-analysis of randomized trials in men with unfavorable-risk prostate cancer, and found significant reductions in prostate cancer mortality and overall mortality, and no significant increase risk of cardiovascular mortality [110]. Despite conflicting results, there is sufficient evidence to suggest a possible increase in cardiovascular risk, and therefore for each man, baseline cardiovascular risk factors need to be considered, and weighed against the likelihood of benefit of ADT on prostate cancer morbidity and mortality. These risk factors should be monitored and managed in those men in whom ADT is initiated. There is no evidence to date that a particular intervention is indicated or will abrogate risk [92].

Dose escalation

Several randomized trials have sought to identify if an improvement in outcome can be achieved by increasing the radiotherapy dose. Prostate cancer is recognized as a relatively radio-resistant malignancy, and doses that can be given are influenced by the tolerance of adjacent normal structures, including the rectum and bladder, and prostatic urethra. Significant technical advances in radiation therapy delivery have enabled safe dose escalation to doses that are less commonly used in other tumor sites. Early radiotherapy to the prostate was delivered using estimations of prostate position based on information from plain X-ray based on correlation to bony landmarks or information from urethrography, and two-dimensional dose calculation. The introduction of 3D conformal radiotherapy was an initial advance. CT anatomical and tissue density information is incorporated for delineation of the target volume and organs and risk, 3D planning systems are used for dose calculation, and customized automated shielding using multi-leaf lead collimators within the treatment head of linear accelerators all allow reduction in the radiation field sizes with better targeting of tumor and lower doses to surrounding normal tissues. An early randomized trial showed the advantage of 3D conformal radiation therapy over 2D techniques in reducing the risk of late proctitis and bleeding, without a reduction in local control [40].

Subsequently, highly conformal techniques have been developed, including intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) and helical tomotherapy (HT). All incorporate computer aided optimization or 'inverse planning' to enable greater conformality. IMRT and VMAT incorporate dynamic variation in dose intensity across beams. Concave dose distributions with steep dose gradients can be achieved. VMAT uses the same hardware (linear accelerators with multi-leaf collimators) with delivery of radiation therapy as the treatment head rotates about the patient, instead of using multiple static beams. HT uses different hardware resembling a CT scanner, with small fan beams delivering treatment while continuously rotating about the patient. These techniques have enabled higher doses to be given to the prostate and seminal vesicles, with the same or lower doses delivered to the rectum and bladder. Early non-randomized data showed that increases in dose up to 86.5 Gy could be achieved with 3D conformal radiation therapy and IMRT. Escalation of dose improved biochemical control, and the use of IMRT enabled this without increasing, or in fact reducing the risk of proctitis [150].

Several randomized trials have been published, all showing reductions in the risk of biochemical relapse with increased dose, a comparison of which is outlined in Table 4 [12, 39, 54, 81, 82, 100, 152]. The majority did not employ highly conformal techniques. In the MDACC trial, subset analysis identified reductions in clinical failure, distant metastases and death from prostate cancer in men with PSA > 10 ng/mL, or with high-risk features [81]. Apart from this subset analysis involving small numbers, none of the randomized trials have shown that improvements in biochemical control translate into an improvement in distant metastases, prostate cancer-specific survival or overall survival.

Kalbasi et al. published results of a retrospective, non-randomized comparative effectiveness study of DERT in men identified with the National Cancer Database (NCDB) [71]. It found that men with intermediate or high-risk disease had improved overall survival if they were treated with doses greater or equal to 75.6 Gy. The limitations of non-randomized trials apply, with multiple potential unknown confounders. A recent meta-analysis of the above randomized

Table 4 Dose escalation—whole organ, < conventional fractionation RCTs

	Participants	Control	Experimental	ADT	Endpoints	Median follow-up	Results
MDACC [82]	1993–1998 $n=301$ T1–3N0M0 PSA pretreatment 'too few pts PSA > 20'; low risk 20/21%; int risk 47/45%; high risk 32/35% (i.e. Predominantly low and int risk	70 Gy 4 field box to 46 Gy (approx. 11 × 11 cm) small field reduction 4 field boost (approx. 9 × 9 cm) to prostate/SV to 70 Gy	78 Gy 4 field box to 46 Gy 6 field 3D conformal boost to prostate/SV to 78 Gy	No	Primary: freedom from clinical or biochemical failure (FFF) (Phoenix includes local, nodal or distant recurrence before PSA failure, and use of salvage ADT) Secondary: overall survival, distant metastases, disease-specific survival	8.7 years	DERT → significant improvement in biochemical or clinical failure: 8 years 78% (DERT) vs 59% No improvement in clinical failure, CSS, OS Subset analysis: FFF reduction limited PSA > 10 ng/mL PSA > 10 ng/mL—8 years FFF 78% (DERT) vs 39%; $P<0.001$; PSA < 10 ng/mL—8 years FFF 78% vs 66%; P 0.237 PSA > 10 ng/mL or high risk: reduced clinical failure, distant metastases, and prostate cancer death
RTOG 0126 [100]	2002–2008 $n=1532$ Intermediate risk (cT1b–2b, GS 2–6 and PSA ≤ 10–20 or GS 7 and PSA < 15)	70.2 Gy/39 3DCRT or IMRT	79.2 Gy/44 3D CRT or IMRT (~ 1/3 conformal)	No	BF (Phoenix)	8 years	No difference in OS DM: HR 0.65 95% CI 0.42–1.01; $P=0.05$ Reduced BF: HR 0.54 (95% CI 0.44–0.65) More salvage ADT in 70.2 Gy arm No difference in acute toxicity More late ≥ grade 2 GU and GI with 79.2 Gy
Dutch (CKTO 96-10) [54]	1997–2003 $N=664$ T1b–4N0	68 Gy 3DCRT 1 cm margin on CTV for PTV	78 Gy 3DCRT 1 cm margin on CTV for PTV to 68 Gy. 0.5 cm margin for 10 Gy boost	Neoadjuvant or adjuvant allowed—~ 20%. Predominantly high risk. Evenly distributed	Primary: biochemical (Phoenix) and/or clinical failure Secondary: clinical failure (CF), local failure (LF), prostate cancer death (PCD) overall survival (OS)	9.2 years	Significant reduction in BF (HR 0.8 95% CI 0.65–0.99; $P=0.046$) No difference in CF, LF, PCD or OS

Table 4 (continued)

	Participants	Control	Experimental	ADT	Endpoints	Median follow-up	Results
GETUG 06 [12]	1999–2002 $n=306$ <75 years; T1b–3aN0M0 with at least one intermediate risk factor, and no more than one high risk factor; PSA < 50 ng/mL (28%/29% high risk)	70 Gy 3DCRT prostate/SV to 46 Gy in 23 boost to prostate 24 Gy	80 Gy 3DCRT prostate/SV to 46 Gy in 23 (10 mm margin, 5 mm post) boost to prostate of 34 Gy (same margin)	No	Primary: biochemical failure (BF; ASTRO and Phoenix) Secondary: overall survival (OS), prostate cancer-specific survival (PCSS), metastasis free survival (MFS), toxicity, QoL	5.1 years	Significant reduction in BF: 5 years BF 39% (70 Gy) vs 28% (80 Gy) ASTRO 5 years BF 32% (70 Gy vs 23.5% (80 Gy) Phoenix no difference in OS, PCSS or MFS toxicity increased with DERT: ≥ grade 2 late GI: 14% (70 Gy) vs 19.5% (80 Gy); $P=0.22$ ≥ grade 2 late GU: 10% (70 Gy) vs 17.5% (80 Gy); $P=0.046$ No difference in QoL
MRC RT01 [39]	1998–2001 $n=843$ T1b–3aN0M0, PSA < 50 ng/mL Low risk 19%, intermediate risk 37%, high risk 43%; balanced	64 Gy in 32 3DCRT prostate/SV (all or base depending on risk), 3 field, 10 mm margin No specified OAR dose constraints	74 Gy in 37 Same to 64/32, with boost to prostate 10 Gy with 6 field	3–6 month neoadjuvant, continued to end of RT LHRH agonist + antiandrogen	Primary: overall survival (OS), biochemical progression-free survival (BPFS) Secondary: salvage ADT, metastasis-free survival (MFS), prostate cancer-specific survival (PCSS), toxicity	10 years	No difference in OS: 10-year OS 71% both. HR 0.99 (95% CI 0.77–1.28); $P=0.96$ Significant improvement in BPFS: 10-year BPFS 43% (64 Gy) vs 55% (74 Gy). HR 0.69 (95% CI 0.56–0.84); $P=0.0003$ Toxicity: Increased ≥ grade 2 GI toxicity 5 years: HR 1.47 (95% CI 1.12–1.92) ≥ Grade 2 GU toxicity 5 years: HR 1.36 (95% CI 0.9–2.06)

Table 4 (continued)

	Participants	Control	Experimental	ADT	Endpoints	Median follow-up	Results
PROG 95-09 [152]	1996–1999 $n = 393$ T1b–2bN0M0 PSA ≤ 15 ng/mL low risk 58%, intermediate risk 37%, high risk 4%; balanced	70.2 Gy in 39 fractions 3DCRT Photons to 50.4 Gy in 28 fractions Proton boost to 19.8 Gy in 11 fractions	79.2 Gy in 44 fractions 3DCRT Photons to 50.4 Gy in 28 fractions Proton boost to 28.8 Gy in 16 fractions	No	Local failure (LF), biochemical failure (BF)(ASTRO), overall survival (OS), toxicity	8.9 years	DERT: reduced LF HR 0.57 Reduced BF: 32.4% vs 16.7% Reduced salvage ADT No difference in OS Increased late toxicity: ≥ Grade 2 GI 12.8% vs 24.6% ≥ Grade 2 GI 24.5% vs 28.2%

trials found significant relationship between dose and biochemical control in all risk groups, but no effect of dose on overall survival [147]. The lack of relationship between biochemical control and clinical failure or survival may be related to the prolonged lag time, effective use of secondary interventions, or competing risks.

The randomized trials of DERT have found increases in toxicity with dose escalation, however, all were conducted before the widespread use of highly conformal radiation techniques, or specified dose constraints for organs at risk. Toxicity outcomes from these trials have contributed to our understanding of dose and volume tolerances for bladder and bowel to keep toxicity acceptably low [1, 56, 114, 119]. Despite the lack of high-level evidence to show that DERT improves survival, based on improvements in biochemical failure, doses above 74 Gy are widely used, and recommended in guidelines [106]. With highly conformal techniques and attention to dose volume constraints for organs at risk, the risk of toxicity can be minimized.

An important consideration with the use of more conformal dose distributions with steep dose gradients and the use of small, tight margins to reduce the dose to the surrounding normal tissues is the risk of geographic miss, or missing the target. Two important advances have addressed this risk: the use of multiparametric MRI for accurate delineation of the prostate, seminal vesicle and organs at risk, and strategies addressing potential organ motion. Multiparametric MRI has contributed not only to better identification of high-risk lesions, but also risk group modification, with frequent upstaging of disease. It allows better identification of extracapsular extension or seminal vesicle invasion, but also better delineation of the prostate from the surrounding normal structures, allowing greater sparing of normal tissues [10, 101]. Accurate image registration with planning CT is essential to ensure these advantages can be realized.

Image-guided radiation therapy (IGRT)

Numerous studies have identified and attempted to quantify interfraction and intrafraction motion of the prostate and seminal vesicles due to variations in bladder and bowel filling, and the implication of this on dose [28, 29, 78, 80, 85, 87, 113, 133, 138]. Failure to take prostate and seminal vesicle motion into consideration can compromise tumor control. A number of studies conducted prior to appreciation of organ movement have found higher relapse rates with more conformal techniques [55, 94]. Numerous studies have shown that increased rectal filling at the time of planning increases the risk of failure, presumably because the prostate moves posteriorly during the course of treatment [37, 57].

Appreciation of this movement has led to strategies to either limit movement, or accurately localize the prostate

for treatment. Bowel and bladder protocols are used in an attempt to limit variation in bladder and bowel filling. Image guidance or image-guided radiation therapy (IGRT) is used to verify the position of the prostate for treatment. Various IGRT methods have been used, including the insertion of triangulated radiopaque intraprostatic fiducial markers into the prostate, transabdominal ultrasound, low dose cone-beam CT scans, insertion of electromagnetic transponders which may allow tracking or gating, or MRI guidance [35, 145]. Tight margins used in highly conformal techniques can only be used if accurate image guidance is employed [84]. Use of daily image guidance may negate the negative prognostic influence of rectal distention at the time of planning [86].

Brachytherapy boost for dose escalation

The randomized trials of dose escalation discussed above all use external beam radiation therapy alone. An alternative mean of escalating dose is with interstitial brachytherapy. Brachytherapy may be delivered either low dose rate (LDR) applications, delivered by permanent insertion of numerous radioactive seeds, including ^{125}Iodine or ^{103}Palladium seeds, or high dose rate applications, delivered using multiple fractions with temporary applicator placement and remote after loading with ^{192}Iridium sources. The advantages of interstitial brachytherapy include the ability to deliver very high doses to the prostate with rapid fall off in dose, with low doses to the surrounding normal tissues, and the ability to overcome the problem of organ motion. Disadvantages include the need for specialized equipment and expertise, and operator dependence. The dose to peri-prostatic tissues, which may harbor microscopic disease, may be insufficient, and therefore it is usually used with external beam radiotherapy for men with intermediate or higher risk features. Not all men have suitable anatomy, and those with high IPSS scores are at higher risk of genitourinary toxicity.

Three randomized trials have reported outcomes of the use of a brachytherapy boost following external beam radiotherapy and are outlined in Table 5. Two relatively small randomized trials have examined the use of high dose rate brachytherapy with ^{192}Iridium [36, 62]. Both identified improvements in biochemical control which have not translated into reductions in metastases or death. Both used suboptimal doses in the control arm by contemporary standards.

ASCENDE-RT is a recently published trial conducted in men with high and intermediate clinically localized prostate cancer. All men were to receive 12 months of neoadjuvant androgen deprivation, with whole pelvic radiotherapy to a dose of 46 Gy in 23 fractions given after 8 months. Men were randomized to receive a conformal external beam boost to 32 Gy in 16 fractions, or a LDR ^{125}I implant to give a minimum peripheral dose of 115 Gy. After a median follow-up of 6.5 years, this has shown that the risk of biochemical failure is more than halved with an LDR boost [105]. No difference in overall survival, prostate cancer-specific or metastasis-free survival was identified. Importantly, LDR brachytherapy leads to significant increases in the risk of late genitourinary toxicity, with more men needing temporary catheterization and/or requiring incontinence pads. The 5-year cumulative incidence of ≥ grade 3 toxicity was 18.4% for LDR boost compared with 5.2% ($P = 0.124$) [128]. Patient-reported health-related quality of life assessments were performed, and identified more clinically significant declines in physical function and urinary function scales in the brachytherapy arm [129].

These trials highlight one of the major limitations of dose escalation alone. More conformal techniques with the use of image guidance enable dose escalation without increasing the dose to nearby rectum, and bowel toxicity may be stable. The prostatic urethra, however, is within the treatment volume, and dose escalation, regardless of the method, will increase its dose and therefore the risk of early and late genitourinary toxicity. Adjustments to seed or catheter placement may minimize the risk, but this may result in some tumor sparing.

An alternative mean of dose escalation that is enabled by newer technologies is partial organ or intra-lesional boosting, or dose-painting. Multiparametric MRI has enabled better delineation of tumor volume, and pathological studies have confirmed that local recurrences occur predominantly at the site of initial involvement [24]. FLAME is a recently published randomized trial examining this approach [103]. Between 2009 and 2015, 571 men with predominantly high risk disease with IPSS ≤ 20 and no TURP within 3 months were randomized to receive 77 Gy in 35 fractions with IMRT, with or without a boost to the tumor defined on multiparametric MRI of up to 95 Gy. Seminal vesicle dose was according to risk, 5–8 mm margins were used for the initial phase, and no margin for boost volume. ADT was permitted and given in 61%. With median follow-up of 4.6 years toxicity outcomes have been reported, showing an increase in the late ≥ Grade 2 GU toxicity, without an increase in GI toxicity. The urethra was not volumed and no dose constraints were specified. The primary outcome, biochemical failure, will be reported with longer follow-up.

With adequate image guidance and tight margins, and partial organ dose escalation, we may be able to avoid increasing rectal toxicity, but it is very difficult to escalate dose without treating prostatic urethra and trigone. These studies suggest that improving outcomes in prostate cancer will rely on more than just increasing the dose, and different approaches are needed to improve the therapeutic ratio. One such strategy aimed at reducing rectal toxicity that is currently under investigation is the insertion of a spacer, such as Space OAR® hydrogel between the prostate and rectum

Table 5 Dose escalation RCTs using brachytherapy boost

	Participants	Control	Experimental	ADT	Endpoints	Median f/u	Results
ASCENDE-RT [105]	2002–2011 $n = 398$ Intermediate and high risk tumors Ineligible if: PSA > 40 ng/mL, T stage ≥ T3b, prior TURP or pre-ADT prostate volume > 75 cm^3	Whole pelvic RT to 46 Gy in 23 fractions 3D conformal boost with 32 Gy in 16 fractions	Whole pelvic RT to 46 Gy in 23 fractions 2–3 week break then ^{125}I LDR brachytherapy implant—minimal peripheral dose 115 Gy	All pts—12 months LHrH agonist and 4 weeks of antiandrogen. RT commencing after 8 months	Primary: biochemical progression free survival (Phoenix) at 5,7 and 9 years Secondary: overall survival, metastasis free survival, prostate cancer specific survival, acute and late toxicity, QoL	6.5 years	Reduction in biochemical failure HR 2.14 (95% CI 1.33–3.45; $P = 0.002$) No difference in overall survival, metastasis-free survival or prostate cancer-specific survival Increased ≥ grade 3 GU toxicity (esp need for temporary catheterization or incontinence pads): 5 years cumulative incidence 18.4% vs 5.2% ($P < 0.001$) Increase in ≥ grade 3 GI toxicity: 5-year cumulative incidence 8.1% vs 3.2% ($P = 0.124$) Among men with adequate erections at baseline, 45% LDR vs 37% report adequate function at 5 years More clinically significant decline in physical function and urinary function with LDR in HRQoL analysis
Hoskin [62]	1997–2005 $n = 218$ T1–3N0M0, PSA < 50 ng/mL, suitable for RT, fit for GA Single center	3D CRT prostate and seminal vesicles to 55 Gy in 20 fractions (hypofractionated) 1.0 cm margins, except post(0.7 cm) Note: relatively low dose	3DCRT prostate and seminal vesicles to 35.75 Gy in 13 fractions followed by HDR boost: 2 × 8.5 Gy in 24 h	Allowed—given in 76% pts—6/12 in low/intermediate Up to 3 years in high risk	Primary: biochemical relapse-free survival (BRFS) Secondary: overall survival, acute and later urinary and bowel toxicity and quality of life (QoL)	10 years	Improvement in BRFS in HDR: HR NR; 10 years 46% HDR vs 39% control ($P = 0.04$) No significant difference in OS: 10 years OS 67% HDR vs 79% control ($P = 0.2$) No difference in severe late urinary or bowel morbidity No difference in QoL

Table 5 (continued)

	Participants	Control	Experimental	ADT	Endpoints	Median f/u	Results
Dayes [36]	1992–1997 $n = 104$ cT2–3pN0 (60% high risk)	EBRT 66 Gy in 33 fractions	^{192}Ir HDR implant 35 Gy over 48 h followed by EBRT 40 Gy in 20 fractions	No, for relapse only	Biochemical failure (Phoenix), time to death, prostate cancer-specific death, metastases	14 years	Significant improvement in biochemical control: HR 0.53 (90% CI 0.31–0.88) No difference in OS, prostate cancer-specific survival or metastases

which can displace the anterior rectal wall outside the high dose region [102]. In a randomized trial with a median follow-up of 3 years, this has been shown to reduce the volume of rectum receiving high dose, and reduce late rectal toxicity and late quality of life declines [51, 95].

Hypofractionation

The above-mentioned trials have used conventional fractionation, with doses per fraction of 1.8–2 Gy. Conventional fractionation is based traditional understanding of the differences in radiobiological responses between most tumors, and late reacting normal tissues, which have a greater capacity to repair sub-lethal damage provided the dose per fraction is kept relatively low. These differences have been quantified by the α/β ratio, being 1-3 for late reacting normal tissues, and closer to 10 for tumors. Numerous investigators have proposed from equi-effective outcomes comparing different dose fractionation schedules that prostate cancer has an α/β ratio closer to 1.5, which is lower than that of nearby late reacting normal tissues [20, 43, 46, 75, 141]. Moderate hypofractionation with the use of larger doses per fraction may have greater biological effect on prostate cancer without increasing late toxicity. It may also significantly shorten the overall treatment time, currently 8–9 weeks for dose-escalated conventionally fractionated treatment.

Several randomized trials comparing moderate hypofractionation with conventional fractionation have been performed, and are compared in Table 6. The majority of participants are of low or intermediate risk. Three large randomized trials have recently reported 5–6-year follow-up. They have largely employed contemporary radiation therapy, with conformal techniques, central quality assurance of target coverage and organs at risk dose volume constraints, and image guidance for accuracy of delivery [23, 38, 91]. CHHIP and PROFIT used hypofractionated doses with similar EQD2 doses to conventionally fractionated control arms [23, 38]. Although both have shown an increase in acute gastrointestinal toxicity with hypofractionation, biochemical failure rates are similar, and there is no increase in late toxicity. Longer follow-up will be required to confirm these findings. Other randomized trials have assessed the effect of dose escalation with hypofractionation using higher EQD2 doses compared with the conventionally fractionated arms [6, 59, 66, 91, 118]. Although one trial found reduced biochemical failure with hypofractionation, the dose in the conventionally fractionated arm was relatively low [59]. Others have not identified reduced biochemical relapse, and importantly have found increased risk of late genitourinary or gastrointestinal toxicity [2, 3, 66, 91]. Sub-group analyses suggest that the risks of late toxicity can be minimized by patient selection and care with dose volume constraints [60,

Table 6 Hypofractionation

	Participants	Control conventional fractionation (CF)	Experimental hypofractionated (HF; $EQD2_{1.5}$)	ADT	Endpoints	Median F/U	Results
CHHiP [38]	2002–2011 $n=3216$ T1b–3aN0M0 Initially PSA < 40, reduced to 30 after 2006, LN risk < 30%. 15% low risk, 73% intermediate risk, 12% high risk	74 Gy in 37 fractions ($n=1065$) 3DCRT or IMRT IGRT allowed but not required No pelvic node RT QA	60 Gy in 20 fractions (77) ($n=1074$) or 57 Gy in 20 fractions (73; $n=1077$) other RT same	3–6 months before and during RT	Primary outcome : biochemical (Phoenix) or clinical failure Secondary: DFS (any prostate cancer related event or death), overall survival, metastases, HT	5.2 years	No difference in biochemical or clinical failure: 5 years: 88.3% CF, 90% (60 Gy), 85.9% (57 Gy) 60 Gy non inferior to 74 Gy: HR 0.84 (90% CI 0.68–1.03) 57 Gy non inferiority not proven: HR 1.2 (90% CI 0.99–1.46) No difference in late toxicity 5 years ≥ G2 GI 13.7% (74) 11.9% (60) 11.3% (57) 5 years ≥ G2 GU 9.1% (74) 11.7% (60) 6.6% (57)
PROFIT [23]	2006–2011 $n=1206$ Intermediate risk (T1–2a, GS ≤ 6 and PSA 10.1–20 ng/mL; T2b–2c, GS ≤ 6 and PSA ≤ 20 ng/mL; or T1–2, GS 7 and PSA ≤ 20 ng/mL)	78 Gy in 39 fractions IMRT encouraged, 3DCRT permitted IGRT SV if risk > 15%; no pelvic RT Central QA	60 Gy in 20 fractions (77) RT same	No	Primary: biochemical–clinical failure-free survival (BCF): (PSA failure (ASTRO), hormonal intervention, local or distant failure, death from prostate cancer Secondary: BCF (Phoenix) Prostate cancer mortality Toxicity HRQoL	6.0 years	No difference in BCF 5 years BCF 85% both arms (HR 0.96 (90% CI 0.77–1.2) No significant differences in late ≥ G3 GU or GI toxicity

Table 6 (continued)

	Participants	Control conventional fractionation (CF)	Experimental hypofractionated (HF; $EQD2_{1.5}$)	ADT	Endpoints	Median F/U	Results
NRG RTOG 0415 [91]	2006–2009 $n=1092$ cT1b–2cN0M0, GS 2–6, PSA < 10 (i.e., Predominantly low risk)	73.8 Gy in 41 (70) 3DCRT or IMRT daily IGRT 4–10 mm margin prostate only ('no attempt to treat seminal vesicles or pelvic lymph nodes')	70 Gy in 28 fractions (80) RT same	No	Primary: disease-free survival (biochemical recurrence (Phoenix), local progression, metastases, or death Secondary: Overall survival, PCSS, LP, adverse events HRQoL	5.8 years	No difference in DFS, with criteria for non inferiority met: HR 0.85 (95% CI 0.64–1.14) No difference in early GI or GU toxicity Increased late ≥ Grade 2 GI and GU toxicity with HF Grade 2/3 GI: RR 1.55–1.59 Grade 2/3 GU: RR 1.31–1.56
HYPRO [66]	2007–2010 $n=804$ T1b–4NX/0MX/0 PSA < 60 ng/mL intermediate or high risk (almost ¾ high)	78 Gy in 39 fractions 95% IMRT 94% IGRT fiducials prostate ± SV according to risk; no pelvic nodes	64.6 Gy in 19 (90.4) same RT Note—3 fractions per week	Permitted 66%/67% median duration 32 months well balanced	Primary: relapse free survival (biochemical relapse (Phoenix), clinical relapse (local or distant), start of HT Secondary: acute and late toxicity, QoL and erectile function	5 years	No significant difference in RFS: HR 0.86 (95% CI 0.63–1.16; $P=0.36$) Similar acute ≥ G2 GU toxicity, but increased GI toxicity with HF Increased late ≥ G3 GU toxicity with HF: 19% vs 13%; $P=0.021$
MDA [59]	2001–2010 $n=206$ T1b–3bN0M0 PSA ≤ 20 ng/mL, GS < 10 (cT3 GS > 7 or PSA > 10 excluded) 27/28% low risk 72/71% intermediate risk	75.6 Gy in 42 fractions (71.2) IMRT IGRT (USS or fiducials) Prostate and proximal SV No pelvic nodal RT	72 Gy in 30 fractions (80.2)	26/23%, < 4 months	Primary: failure (biochemical failure (Phoenix) or salvage therapy	8.5 years	Lower BF with HF: HR NR. $P=0.036$ 8 years BF 10.7% CF (95% CI 5.8–19.1%) vs 15.4% (95% CI 9.1–25.4%) No difference in OS No difference in late GU toxicity Non-significant increase in late ≥ G2 GI toxicity: 8 years 5% vs 12.6%; $P=0.08$) Late GI toxicity HF arm 8.6% if V65 Gy ≤ 15%

Table 6 (continued)

	Participants	Control conventional fractionation (CF)	Experimental hypofractionated (HF; $EQD2_{1.5}$)	ADT	Endpoints	Median F/U	Results
Arcangeli [6]	Single institution 2003–2007 $N = 168$ High risk	80 Gy in 40 fractions 8 weeks 3DCRT prostate and SV	62 Gy in 20 fractions (81) in 5 weeks	All—9 months, RT starting after 3 months	Primary outcome: late toxicity Secondary: freedom from biochemical failure (FFBF), PCSS, OS	9 years	No significant difference in freedom from late ≥ G2 toxicity: GU: 86% (CF) vs 79% (HF) GI: 86.5% (CF) vs 84.6 (HF) Non-significant trend toward improved FFBF, PCSS with HF No difference in OS
Pollack [118]	2002–2006 $n = 303$ ~65% intermediate risk, ~35% high risk	76 Gy in 38 fractions IMRT Prostate/prox SV Distal SV and pelvic nodes for high risk	70.2 Gy in 26 fractions (84.2)	Long term (24 months) for high risk, short term for intermediate risk	Primary: biochemical disease-free survival (BF (modified ASTRO), clinical failure, salvage therapy) Acute and late toxicity	5.7 years	No difference in BDFS: no difference in local or distant failure, PCSS or OS No statistically significant differences in acute or late toxicity, Higher risk of late GU toxicity with HF with baseline IPSS > 12

118]. Only one trial included patients treated with pelvic nodal irradiation, treating just over 30% of participants who had high-risk disease. This was a risk factor for increased late genitourinary toxicity.

The above trials suggest that with modern radiotherapy techniques, using highly conformal techniques, using small margins and image guidance to ensure treatment accuracy and reduced dose to normal tissues, hypofractionated radiotherapy is effective with an acceptable toxicity profile, and allows a significant reduction in the overall treatment time, inconvenience and resource utilization. Bearing in mind that the larger contemporary trials report follow-up in the order of 5–6 years, and that < 20% of participants of the above trials had high risk disease, on the basis of the results reported to date, the most recent ASTRO/ASCO/AUA and AUA/ASTRO/SUO guidelines recommend that moderate hypofractionation be considered for men of any risk category who are suitable for radiotherapy [104, 130]. Although the different dose fractionations have not been compared, there is more evidence to support doses of 60 Gy in 20 fractions or 70 Gy in 28 fractions, with doses higher than these associated with greater late toxicity based on the above trials. Longer follow-up will be essential to determine the optimal fractionation, and whether efficacy and toxicity vary according to baseline characteristics.

Stereotactic radiation therapy

While the above trials have explored 'moderate' hypofractionation, there is interest in more extreme hypofractionation, referred to as stereotactic body radiation therapy (SBRT) or stereotactic ablative radiation (SABR). These involve the use doses per fraction closer to 6–9 Gy, with total EQD2 of 86-168 Gy, although the linear quadratic equation is unlikely to predict cell kill at such high doses per fraction [76]. It is thought that endothelial damage, and possibly immune effects contribute to the cell kill with these high doses per fractions [47]. Safe delivery of SBRT relies to an even greater degree on technological advances mentioned above, including highly conformal inverse planning techniques, improved imaging, image guidance and strategies to address intrafraction movement. Ideally additional incorporation of radiofrequency tracking technology, using implanted markers by which intrafraction movement can be monitored, is required. A number of investigators have published their experience, largely with low or intermediate risk disease, suggesting lower biopsy positivity and PSA nadirs, but with increases in GU and GI toxicity [93]. There has been insufficient follow-up for mature biochemical failure outcomes. Until adequately powered randomized trials with sufficient follow-up are reported, SBRT should be considered investigational, and enrollment to clinical trials encouraged.

There is extensive interest in the use of SBRT in the treatment of oligometastatic prostate cancer. To date, this approach has proved feasible and safe when dose volume constraints are respected, and appears to delay time to salvage androgen deprivation treatment.

Whole pelvic radiation therapy (WPRT; elective nodal irradiation)

An additional strategy employed in an attempt to improve the chance of cure with external beam radiotherapy is elective nodal irradiation of pelvic nodes, or whole pelvic radiotherapy (WPR). There are a number of theoretical arguments to support the elective treatment of pelvic nodes. Surgical lymphadenectomy studies have identified microscopic, radiologically occult, nodal metastases, especially with higher risk tumors [22]. The Roach formula, (LNI risk = 2/3 PSA + [(GS-6) × 10]) based on PSA and Gleason score was validated on surgical series and stratifies men at low or high risk of nodal metastases [126]. Lymph node drainage studies reveal the wide drainage patterns of the prostate to pelvic nodal groups including external, internal and common iliac, obturator and presacral nodes [97]. The RTOG 9202 trial confirming improved survival with long-term androgen deprivation used whole pelvic radiotherapy [89]. Finally, patterns of failure studies after prostate and seminal vesicle only radiotherapy show high incidence of pelvic node recurrence, including in common iliac nodes [135].

There are, however, a number of arguments against elective pelvic nodal irradiation. Increasing the treated volume has the potential to increase toxicity. Treatment of the whole pelvis with 3D conformal radiotherapy includes large volume of small and large bowel. Highly conformal techniques allow significant reduction in dose to bowel [111, 142]. Many debate whether nodal metastases are curable with the doses of radiation that can be employed, even with additional androgen deprivation. Finally, three randomized trials, outlined in Table 7, have failed to reveal significant effects on biochemical failure, clinical failure or survival [7, 8, 88, 120, 125].

The early RTOG 77-01 included many men with lower risk disease, including those who were pathologically node negative. The subsequent RTOG 94-13 trial was conducted in men thought to be of high risk of lymph node metastases on the basis of Roach formula LN% greater than 15%. This was a 2 × 2 randomized trial, with randomization either to prostate/seminal vesicle radiation therapy (PORT) or WPRT, and randomization to 4 months of neoadjuvant or adjuvant androgen deprivation. Although the initial analysis after a median follow-up of almost 5 years found a significant

Table 7 Whole pelvic radiotherapy

	Participants	Control	Experimental	ADT	Endpoints	Median f/u	Results
RTOG 7706 [7]	T1b–2N0M0 (nodes staged lymphangiography)	64.8 in Gy in 36 fractions prostate bed	WPRT to 45 Gy in 25 Boost to prostate to 64.8 Gy			7 years	No difference in local control, disease-free survival or overall survival
RTOG 9413 [88]	1995–1999 $n=1292$ LNI risk > 15% (Roach), PSA ≤ 100 ng/mL 73% GS ≥ 7	4 field box, urethrogram to localize prostate 70.2 Gy in 39 fractions limit field size < 11 cm × 11cm	4 field box WPRT to 50.4 Gy in 28 fractions superior limit L5/S1 Boost to prostate/SV of 19.8 Gy in 11 fractions	2 × 2 design: all 4 months of total androgen suppression (goserelin or leuprolide + flutamide) Randomized to neoadjuvant or adjuvant	Powered for comparison NHT vs ADT and PORT with WPRT Primary endpoint: progression-free survival (PFS) = BF (ASTRO and Phoenix)	12 years	No significant difference in PFS comparing WP with PORT or NHT with ADT Suggested interactions between field size and use of NHT vs ADT—less clear with longer follow-up No significant difference in late ≥ G3 GU toxicity Increased late ≥ G3 GI toxicity in WP/NHT (5% WPRT/NHT vs 1% PO/NHT, 2% WPRT/AHT, 2% PORT/AHT)
GETUG-01 [121]	1998–2004 $n=444$ T1b–3N0pN × M0 stratified by risk (low risk: cT1c–2c, GS ≤ 6, PSA < 3 × ULN; high risk cT3, GS ≥ 7, PSA > 3 × ULN) ~ 50% GS 6 > 50% LNI risk < 15% (Roach)	3DCRT, 4 field prostate to 66 Gy (increased to 70 Gy after 2000) Mean total dose 68 Gy Seminal vesicle to 46 Gy in uninvolved, 60 Gy if involved (other fractionation permitted 1.8–2.25 Gy/f)	3DCRT 4 field WPRT to 46 Gy; superior limit at S1/2 Boost to prostate/SV to same dose as control	Permitted high risk—4-8 months neoadjuvant and concomitant	Primary: event free survival (BF (ASTRO) or local or distant progression)	11.4 years	No difference in 10-year EFS or OS Post hoc analysis suggested benefit of WPRT in low-risk group, not receiving ADT No significant differences in toxicity

reduction in biochemical failure with WPRT, no significant difference was evident on a subsequent analysis with longer follow-up. The initial analysis had suggested an interaction between the use of WPRT and the timing and androgen deprivation, with significant reductions in failure in men receiving neoadjuvant hormones who receive WPRT compared with PORT. These differences did not remain significant with longer follow-up, and indeed the trial was not powered for comparison between the four treatment arms. The GETUG-01 was also negative, but also included many men of lower risk.

The failure to identify improvements in outcome with whole pelvic radiotherapy may be related to poor patient selection, inadequate coverage of nodes or inadequate dose. The use of highly conformal techniques necessitates accurate delineation of nodal locations at risk, and consensus guidelines have been published [53, 90]. There is ongoing debate about the adequacy of these volumes, with a recent MSKCC pattern of failure trial after prostate and seminal vesicle only found a high incidence of common iliac relapse [97].

There is concern that highly conformal dose distributions for pelvic nodes may lead to compromised coverage depending on the image guidance used. Image guidance is often based on the position of the prostate, rather than bony anatomy and pelvic nodal position. Despite this, studies suggest that the risk of failing to cover the nodal PTV due to image guidance based on fiducials is very low, although this would depend on margins used [44, 64].

The results of the ongoing RTOG 09-24, in men of moderate to high risk of recurrence, using contemporary radiotherapy techniques with IMRT, contemporary doses (to 79.2 Gy or brachytherapy implant) and 4, 6 or 32 months of androgen deprivation, and the UK prostate and pelvis versus prostate alone treatment for locally advanced prostate cancer (PIVOTAL) trial, a multicenter phase II trial, are eagerly awaited.

Although there is interest in hypofractionated whole pelvic radiotherapy, the above studies have used conventional fractionation [70]. Only the Italian randomized trial of hypofractionation used whole pelvic radiotherapy [6].

Adjuvant systemic therapy

An important reason for failure to cure prostate cancer with radiotherapy may be related to occult metastatic disease. As mentioned above, numerous studies have confirmed the benefit of the addition of ADT to radiation therapy, either because of a synergistic effect with increased radiosensitivity, or effects on micro-metastatic disease. A significant proportion of men with high-risk disease fail despite the use of DERT, neoadjuvant and long-term adjuvant ADT, and alternative strategies are required. A number of systemic agents have been investigated in an attempt to target occult metastatic disease. Based on its efficacy in the setting of metastatic castration-resistant prostate cancer (PRPC) in TAX 327 and subsequently in hormone naïve metastatic disease in CHAARTED and GETUG-AFU 15, docetaxel has been used earlier with radiation therapy and ADT with high risk, non-metastatic disease [49, 136, 137]. Four randomized trials are compared in Table 8 [45, 67, 74, 131]. Although STAMPEDE found an improvement in median survival with the addition of docetaxel, subset analysis did not show a benefit in the M0 subset. Longer follow-up is required to determine if there are significant improvements in survival that would justify the toxicity of docetaxel.

Newer agents, which act on the androgen receptor, such as enzalutamide, a potent androgen receptor inhibitor, are also being investigated, based on their activity in the metastatic setting, and more favorable side effect profile with randomized trials in progress.

Imaging advances

New staging imaging modalities such as positron emission tomography (PET) using prostate-specific membrane antigen (PSMA) ligands have shown promise in the detection of otherwise occult metastatic disease. Staging for metastatic disease for intermediate and high-risk men at initial presentation has traditionally included computed tomography (CT) scans of the abdomen and pelvis for detection of lymph node metastases, MRI for identification of local recurrence, and ^{99m}Tc bone scans for bony metastatic disease. The sensitivity and accuracy of CT, or MRI, for detection of lymph node involvement are low [21, 63]. While not yet widely available, the sensitivity, specificity and accuracy of PET imaging with PSMA ligands have been shown to be superior to morphological staging with CT or MRI using histopathological correlation of lymph node dissection [98, 99, 123], and superior to bone scan in the detection of bone metastasis, although histological confirmation of metastatic disease is often lacking [122]. Currently, early deaths in clinical trials may be the result of comorbid conditions or occult metastatic disease at presentation. More widespread use of accurate imaging for staging will better identify those with metastatic disease for whom radical local treatment will not be curative, and for whom alternative strategies are required, and those with truly localized disease for whom intensification of local therapy is justified. Improved staging will result in stage shifts that will need to be considered when comparing outcomes from contemporary series with historical controls.

Table 8 Adjuvant docetaxel

		Control	Experimental	Local treatment/RT	Median f/u	Results
GETUG 12 [45]	2002–2006 $n=413$ High risk ≥ GS 8 or T3 or 4 or PSA ≥ 20 ng/mL, or N + ve M0	ADT 3 years LHRH + 3 weeks antiandrogen	ADT 3 years + 4 cycles of docetaxel and estramustine	If N0—radical prostatectomy or RT (3DCRT to 70–78 Gy, start after 3 months chemo)	8.8 years	Reduced biochemical failure with chemo No OS difference
RTOG 0521 [131]	2005–2009 $n=612$ High risk (PSA > 20 < 150 ng/mL or GS 8–10	ADT	ADT + 6 cycles of docetaxel and prednisone starting 28 days after RT	IMRT option WPRT 46.8 Gy, boost to prostate and seminal vesicles to 75.6 Gy	5.5 years	4-year OS 89% (ADT alone) vs 93% (ADT + chemo) HR 0.68 (95% CI 0.44–1.03)
STAMPEDE [67]	2005–2013 $n=2962$ high risk locally advanced non-metastatic (T3–4, PSA ≥ 40 ng/mL or GS 8–10) or newly diagnosed N+ or M1 15% N+, 24% M0	3 years ADT	Same ADT + 6 cycles docetaxel, 2 years of zoledronic acid, or both	RT at discretion treating physician N + WPRT 3DCRT or IMRT	3.6 years	Improvement in median survival with docetaxel, but not zoledronic acid Subset analysis—no survival benefit in M0
SPCG-13 [74]	$n=376$	Neoadjuvant/adjuvant ADT	Same ADT + 6 cycles docetaxel		5 years	No difference in biochemical failure

Conclusion

Identifying the optimal treatment for each man with prostate cancer remains a significant challenge. Although some tumor and patient factors allow us to make some estimate of competing risks, prostate cancer behavior is heterogenous. For many men, prostate cancer has a long disease course. Identification of optimal treatment cannot rely on comparison of biochemical relapse alone. While it does provide an early marker of relapse, it is not a surrogate for prostate cancer morbidity, and provides no indicator of treatment-related morbidity. Reporting of toxicity outcomes has been incomplete and non-standardized, particularly for incontinence and sexual dysfunction. Given the long natural history of prostate cancer, efficacy and toxicity outcomes of randomized trials that have reported clinically relevant outcome data now will not have used currently available staging imaging investigations, and may have used radiation therapy techniques that do not reflect contemporary practice. For those for whom a decision to use definitive external beam radiotherapy is made, there are numerous strategies employed to optimize outcomes, either aimed at improving efficacy or reducing toxicity. The optimal strategy, or combination of strategies for each man is debatable, and hopefully will be elucidated with ongoing trials using not only efficacy outcomes and standardized toxicity measures, but patient-reported outcomes. In the meantime, presenting the different options and the evidence clearly to each man is important, if challenging, and will allow him to make an informed choice that takes into account his personal preferences.

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Compliance with ethical standards

Conflict of interest The author has no conflict of interest to declare.

Ethical standards This review includes no person-level information and therefore no consent or ethical committee review was required.

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