Radiotherapy in the Management of Prostate Cancer

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Contents

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Abstract

Prostate cancer remains one of the most common cancer diagnoses among men in North America. The majority are treated with surgery or radiotherapy; and the advent of technological precision has driven remarkable improvements in clinical outcomes. Here, we highlight existing controversies surrounding the use of radiotherapy in the management of prostate cancer, with specific focus on different clinical scenarios.

1 Background

Each year, 1.1 million men are diagnosed with prostate cancer (CaP) worldwide. Based on documented global incidence patterns, the diagnosis of CaP is more common in the Western part of the world, contributed in part by the advocacy of routine prostate-

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specific antigen (PSA) screening in men, despite the lack of supportive evidence (Potosky et al. 1995). Inadvertently, this has led to an increase in the number of patients receiving definitive treatment for organ-confined CaP, along with concerns of overtreatment in some of these men (Welch and Albertsen 2009; Cooperberg et al. 2010; Mitchell 2013).

A well-established mechanism for stratifying patients who are diagnosed with CaP involves assessing PSA, Gleason score (GS) and primary tumour extent (T category) (D'Amico et al. 1998) and classifying patients into low- , intermediate- or high-risk categories based on these clinical and pathological indices. Nonetheless, significant inter-patient heterogeneity exists within each risk category, and recent NCCN guidelines have been updated to include additional very low- and very high-risk categories to address this issue (Mohler et al. 2014). For the majority of indolent localised CaP, treatment options include radical prostatectomy (RadP), radiotherapy (RT) and active surveillance (intended for patients with low-risk disease) (Wilt et al. 2012). High-quality retrospective evidence have suggested equivalence in terms of tumour control and toxicities between RadP and RT, but this remains a debatable issue given the paucity of level I randomised evidence (D'Amico et al. 1998; Grimm et al. 2012; Resnick et al. 2013; Sooriakumaran et al. 2014).

Regarding the choice of RT technique, external beam treatment and brachytherapy are proven alternatives (D'Amico et al. 1998; Koukourakis et al. 2009; Peinemann et al. 2011). Brachytherapy modalities include low-dose rate (LDR) monotherapy (permanent radioactive iodine seed (I^{125}) insertion) or interstitial implant insertion for remote afterloading high-dose rate (HDR) boost following external beam RT (Galalae et al. 2004; Martinez et al. 2002, 2011; Hoskin et al. 2012; Morton et al. 2011). With regard to external beam treatment, there are, at present, a variety of options with intensity-modulated RT (IMRT), image-guided RT (IGRT), proton RT and stereotactic body RT (SBRT). These technological advances offer precise irradiation of the prostate gland, leading to significant reduction in late RT-induced adverse events (Sheets et al. 2012). Nonetheless, while clinical outcomes of CaP patients following RT have been mostly favourable, several issues covering various aspects of treatment remain widely debated. Among these are arguments pertaining to elective pelvic nodal irradiation, the use of dose escalation and hypofractionation and the choice of patients for RT as opposed to RadP and vice versa. In this chapter, we shall review and discuss the prevailing controversies in the RT management of CaP.

2 The Role of Radiotherapy in PSA Screening-Detected Prostate Cancer

Evidence from two large PSA screening trials have both highlighted the significant health burdens associated with overdiagnosis (Schröder et al. 2009, 2012, 2014; Andriole et al. 2009, 2012; Heijnsdijk et al. 2012). While the North American PLCO study failed to demonstrate a mortality reduction in men who have been subjected to PSA screening, the companion European ERSPC study was positive in demonstrating that numbers needed to screen to avoid one CaP death continue to fall over time (Schröder et al. 2014). Nonetheless, there is also recognition that PSA is a 'poorly' predictive test for CaP, due to its intrinsic high false positivity. For example, between 10 and 70% of men across the different study sites in ERSPC had a positive PSA test, but a negative pathological diagnosis. It is very likely that complementation with other non-invasive measures such as multiparametric MRI or urine prostate cancer antigen 3 (PCA3) is required to enhance the value of PSA screening, and these strategies await testing.

In the same period, two other randomised trials were conducted to query if upfront RadP conferred a survival benefit over watchful waiting in patients with organ-confined CaP (Bill-Axelson et al. 2011, 2014; Wilt et al. 2012). Similar to the PSA screening studies, conflicting results were reported. In the Swedish study by Axelson et al. (SPCG-4), early surgery was associated with a reduction in CaP deaths, with the largest benefit being observed in patients harbouring intermediate-risk disease (Bill-Axelson et al. 2011, 2014). Conversely, in the trial by Wilt et al. (PIVOT), no difference in survival outcomes was observed between early surgical intervention and

observation, except in patients with a presenting PSA of >10 ng/ml (Wilt et al. 2012). A key disparity between the trials, which could perhaps explain the contrast in results, relates to the time period when these studies were initiated. Unlike SPCG-4 that commenced prior to the PSA screening era, the majority of patients from PIVOT had been PSA screened, which is in keeping with the observation of less advanced disease, corresponding to fewer cancer deaths in the latter trial (proportion of T1c tumours was 12%, SPCG-4 vs. 50%, PIVOT; CaP-specific mortality was 19.6% vs. 7.1%, respectively).

Currently, there is a massive effort by the UK study group to address (1) the role of PSA screening (CAP) and (2) active surveillance against either RadP or RT in the management of PSA screening-detected CaP (ProtecT) (Lane et al. 2010, 2014). Results of the latter trial should be available in 2016. Until then, it may not be unreasonable to extrapolate evidence from the surgical-based studies to the RT patient, if we were to assume equipoise between RT and RadP. Treatment-related mortality is unquestionably low with RT. Rather, in the majority of men who have been treated for CaP, competing non-CaP causes of deaths are not negligible (Roobol and Bokhorst 2014). As evidenced in the PIVOT trial, only a mere 52 patients (7.1%) died from CaP compared to 354 (48.4%) deaths from all other causes (Wilt et al. 2012). It is thus pertinent in contemporary clinical practice to consider factors such as expected life expectancy and patient's expectations prior to consenting them for treatment. Development of methods to identify non-indolent CaP is also important to ensure treatment is not inappropriately withheld. In this regard, multiparametric MRI and molecular tumour profiling are promising potential approaches (van den Bergh et al. 2014; Lalonde et al. 2014).

3 Dose Escalation in Localised Prostate Cancer

The earliest work supporting a dose-response above 60 Gy in localised CaP included published reports by Zelefsky et al. (1998). In their prospectively collected series, planned radiation doses to the entire prostate gland were gradually increased from 64.8 to 81.0 Gy, and a dose-response relationship was established for both PSA nadir and control, with the most striking effect being observed in intermediate- and high-risk disease. Other benefits of dose escalation that have been demonstrated subsequently include reduction of local relapses, distant metastases and CaP-specific mortality (PCSM) (Zelefsky et al. 2011; Kuban et al. 2011).

There are now several large randomised trials that have investigated the implications to survival and toxicities with dose escalation. Mature results of these studies are summarised in Table 1. Pollack et al. conducted a trial of 78 vs. 70 Gy and observed superior biochemical control and a reduced likelihood of distant relapses and CaP deaths with 78 Gy. In a subgroup analysis, those <70 years of age and PSA of >10 ng/ml benefited most from the higher dose (Pollack et al. 2000, 2002; Kuban et al. 2008, 2011). The improvement in biochemical control is consistent across all studies, with reported gains of 10–25% (Al-Mamgani et al. 2008; Heemsbergen et al. 2014; Zietman et al. 2010; Beckendorf et al. 2011; Dearnaley et al. 2014; Michalski et al. 2014, 2015).

Nonetheless, the strongest argument against dose escalation in localised CaP points to the blatant fact that none of the studies demonstrated an associated overall survival (OS) advantage. In the most recent report of RTOG 0126, where nearly 1,500 men with intermediate-risk CaP were randomised to 79.2 vs. 70.2 Gy, a 7-year OS was comparable between both cohorts (HR 0.98 [0.79–1.21]) (Michalski et al. 2014, 2015). This, despite significant improvements across all other clinical endpoints (including reduction of distant metastasis) with dose escalation in RTOG 0126. Again, competing causes of death significantly confounded the potential benefit of PCSM reduction with dose escalation (3%, PCSM, vs. 19.8%, other competing causes). Thus, it is clear that prudent selection of patients for dose escalation is required. A nice example for this is provided by Kuban et al. where they demonstrated in their post-hoc analysis of the MD Anderson trial that benefits of dose escalation were limited to high-risk patients who are <70 years old (Kuban et al. 2011). Another analysis of 1,060 men from

Table 1 Overview of main characteristics and findings of radiotherapy dose-escalation trials for localised prostate cancer

Trial	Start	*N*	Patients	RT dose levels	ADT	Median follow-up	Main finding (control group vs. dose-escalated group)	Toxicity (control group vs. dose-escalated group)	Publication
MRC RT01 (UK)	1998	843	IR: 37% HR: 43%	64 Gy in 32 fractions vs. 74 Gy in 37 fractions	All pts received neoadjuvant ADT for 3–6 months	10 years	10-year BPFS 43% vs. 55%, ($p = 0.0003$) 10-year OS 71% for both groups ($p = 0.96$)	5-year late GU grade ≥ 2 8% vs. 11% ($p = 0.056$) Late GI grade ≥ 2 24% vs. 33% ($p = 0.055$)	Dearnaley et. al. 2007, 2014
MDACC 93-002	1993	301	IR: 46% HR: 34%	70 Gy in 35 fractions vs. 78 Gy in 39 fractions	No	8.7 years	8-year FFBF 59% vs. 78% ($p = 0.004$) 8-year FFDM 95% vs. 99%, ($p = 0.059$) 8-year OS 78% vs. 79%, ($p = 0.315$)	Late GI grade ≥ 2 13% vs. 26%, ($p = 0.013$) Late GU grade ≥ 2 8% vs. 13%, (p = NS)	Pollack et. al. 2002 Kuban et. al. 2008
PROG 95-09	1996	393	LR:58% IR: 37% HR: 5%	70.2 GyE in 39 fractions vs. 79.2 GyE in 44 fractions (proton boost)	No	8.9 years	HR 0.57 for local failure in dose-escalation group 10-year BFR 32.0% vs. 17.4% ($p = 0.0001$) 10-year OS 78.4% vs. 83.4% ($p = 0.41$)	Late GU grade ≥ 3 2% Late GI grade ≥ 3 1% (both groups, p = NS)	Zietman et. al. 2010
Dutch trial (CKTO 6910)	1997	664	IR: 27% HR: 55%	68 Gy in 34 fractions vs. 78 Gy in 39 fractions	Yes, 22% of pts	9.2 years	BFR 46% vs. 52% ($p = 0.025$) CFR 34% vs. 37% ($p = 0.4$) PCD 13% vs. 13% ($p = 0.8$) OS 31% vs. 30% ($p = 0.9$)	7-year late GU grade ≥ 2 40% vs. 41% ($p = 0.6$) Late GI grade ≥ 2 25% vs. 35% ($p = 0.04$)	Al-Mamgani et. al. 2008 Heemsbergen et. al. 2014

Trial	Start	*N*	Patients	RT dose levels	ADT	Median follow-up	Main finding (control group vs. dose-escalated group)	Toxicity (control group vs. dose-escalated group)	Publication
RTOG 0126	2002	1,532	70% had PSA < 10 ng/ml, 84% with GS 7, 57% had T1 disease	70.2 Gy in 39 fractions vs. 79.2 Gy in 44 fractions	No	7 years	10-year OS 66% vs. 67% ($p = 0.87$) BFR 43% vs. 26% ($p < 0.0001$) LPR 8% vs. 4% ($p = 0.0059$) DMR 8% vs. 5% ($p = 0.026$) STR 21% vs. 13.5% ($p = 0.0002$)	Late GU/GI grade ≥ 2 37% vs. 45% ($p = 0.0012$) Time to late GI grade ≥ 3 was higher for the 79.2 Gy arm ($p = 0.035$) but time to late GU grade ≥ 3 toxicity was not ($p = 0.14$)	Michalski et. al. 2015
GETUG 06	1999	306	HR: 29%	70 Gy in 35 fractions vs. 80 Gy in 40 fractions	No	5 years	BRR 39% vs. 28% ($p = 0.036$)	Late GU grade ≥ 2 10% vs. 17.5% ($p = 0.046$) Late GI grade ≥ 2 14% vs. 19.5% ($p = 0.22$)	Beckendorf et. al. 2011

ADT androgen deprivation therapy, *MRC* Medical Research Council, *IR* intermediate risk, *HR* high risk, *BPFS* biochemical progression-free survival, *OS* overall survival, *GU* genitourinary, *GI* gastrointestinal, *MDACC* MD Anderson Cancer Centre, *FFBF* freedom from biochemical failure, *FFDM* freedom from distant metastasis, *NS* not significant, *GyE* Grey Equivalent, *HR* hazard ratio, *BFR* biochemical failure rate, *BFR* biochemical failure rate, *CFR* clinical failure rate, *PCD* prostate cancer death, *PSA* prostate-specific antigen, *GS* Gleason score, *LPR* local progression rate, *DMR* distant metastasis rate, *STR* salvage therapy rate, *BRR* biochemical relapse rate

British Columbia also suggested that better biochemical control post-RT was only associated with prolonged survival in individuals with ≥10-year life expectancy (Herbert et al. 2012).

Moreover, dose escalation is not without risks, as evidenced by the increased likelihood of late adverse effects to the rectum and bladder. Fortunately, severe (RTOG grade 3) late effects were not always more frequent. Modern technologies like IMRT and IGRT are also useful tools in mitigating risks of late toxicities imposed by dose escalation (Al-Mamgani et al. 2009; Sheets et al. 2012; Michalski et al. 2013).

Going forward, an improved schema of selecting patients for dose escalation is desperately needed. An example would be dichotomising intermediate-risk patients into favourable and unfavourable subgroups using additional pathological indices (percentage of core positivity and a predominant GS 4 pattern) and testing if this manner of stratification predicts for better outcomes with dose escalation (Zumsteg et al. 2013).

This issue of dose escalation is further complicated by the synergistic effects of androgen deprivation and RT. It is generally agreed that combination androgen deprivation is synonymous with a dose-escalation effect. Several randomised studies of combined modality treatment have confirmed this hypothesis (Bolla et al. 2002; D'Amico et al. 2004; Denham et al. 2005; Lawton et al. 2007; Horwitz et al. 2008; Jones et al. 2011), but we still lack information on the optimal RT dose in the setting of combined treatment. The UK-led MRC RT01 study reported a subgroup analysis where high-risk patients had a better biochemical relapse-free rate (bRFR) with RT of 74 Gy vs. 70 Gy in combination with 6 months of androgen deprivation, but no impact on OS was observed (Dearnaley et al. 2014). EORTC 22991 and the Quebec study formally test both parameters in a 2 × 3- (70 Gy vs. 74 Gy vs. 78 Gy, with or without 6 months of androgen deprivation) and 2 × 2- (70 Gy vs. 76 Gy, with or without 6 months of androgen deprivation) study design, respectively (Bolla et al. 2014; Nabid et al. 2015). Results of these studies will inform on the optimal strategy, as well as provide scientific insights into the molecular interactions between androgen deprivation and RT.

4 RT Versus Radical Prostatectomy in High-Risk Prostate Cancer

There is limited evidence to conclude if RT or RadP ought to be the treatment of choice in men with high-risk CaP. Retrospective evidence may suggest equipoise between them in terms of survival and preventing clinical progression, but proponents of RadP often argue on the grounds of detailed pathological staging and accurate prognostication (Boorjian et al. 2011; Parikh and Sher 2012). The potential of a decreased likelihood of distant metastasis with RadP has also been suggested (Porter et al. 2006; Zelefsky et al. 2010). A recent meta-analysis comparing RadP and RT had included 19 retrospective studies with differing levels of confounding biases and drew the conclusion that RT is associated with a poorer OS and a higher rate of PCSM compared to RadP (Wallis et al. 2015). It should however be cautioned that nearly every retrospective study comparing RadP vs. RT in the treatment of CaP is inherently weakened by open or hidden biases that may not be easily managed by any statistical means, including propensity score matching.

Nonetheless, on the backbone of recent evidence generated by several randomised trials, the current standard regime for high-risk CaP patients treated with RT involves combined androgen deprivation (Bolla et al. 2002; D'Amico et al. 2004; Denham et al. 2005; Lawton et al. 2007; Horwitz et al. 2008; Jones et al. 2011). The consensus also agrees that optimal duration of androgen deprivation is between 18 and 36 months for high-risk patients (Nabid et al. 2013; Bolla et al. 2009; Horwitz et al. 2008; Zapatero et al. 2015). In patients who are already on long-term androgen deprivation, irradiation of the prostate confers a twofold reduction in CaP deaths and an estimated 8–15% improvement in OS, persisting even after 8 years (Widmark et al. 2009; Warde et al. 2011; Mason et al. 2015). A recent meta-analysis confirmed the efficacy of combined modality therapy against either single-modality hormonal therapy or RT (Schmidt-Hansen et al. 2014). Thus, the prevailing dilemma remains determining the right patients for RadP or combination hormonal RT. A fine illustrative example is a 65-year-old healthy man who is diagnosed with low volume, cT2a

(peripheral zone tumour on MRI), PSA 15 ng/ml, but GS 9 (on targeted biopsy), and intraductal carcinoma-associated CaP, for which either option can be resoundingly argued for and against.

5 Elective Whole Pelvis Radiotherapy in Node-Negative Disease

Although the indication for prostate RT is definitive in patients harbouring localised high-risk disease, the same cannot be said for prophylactic irradiation of the pelvic lymph nodes. To date, three randomised trials (RTOG 77-06, 94-13, GETUG-01) have examined if irradiating the pelvic lymph nodes conferred OS or bRFR benefits in CaP, none of which yielding any positive findings (Asbell et al. 1988, 1998; Roach et al. 2003; Pommier et al. 2007) (Table 2). In reality, the strongest evidence supporting the role of empirical pelvic irradiation comes solely from several retrospective series (Seaward et al. 1998a, b; Pan et al. 2002; Jacob et al. 2005; Aizer et al. 2009; Milecki et al. 2009; Mantini et al. 2011).

RTOG 77-06 was the first of three trials, conducted prior to the implementation of PSA screening and D'Amico risk stratification. Briefly, patients with node-negative organ-confined CaP, ascertained by radiology or surgical staging, were randomised to receive prostate RT with or without whole pelvis RT. OS was comparable between both arms, even after a long follow-up duration of 12 years (Asbell et al. 1998). However, a significant proportion of the study participants (approximately 80%) had favourable GS, which would have portended for a low risk of nodal metastasis, thus raising the question if pelvic RT should have been indicated in the first place.

RTOG 94-13 was a more contemporary study designed to address two key issues simultaneously. Apart from testing the hypothesis that pelvic RT improves progression-free survival (PFS) in patients with CaP, it also examined the impact of neoadjuvant vs. adjuvant sequencing of androgen deprivation. Rather appropriately as opposed to RTOG 77-06, patient selection was performed based on a ≥15% risk of nodal metastasis estimated using the Roach's equation (Roach et al. 1994). In the initial report, patients who were randomised to whole pelvis RT (WPRT) and neoadjuvant hormonal therapy (NAHT) experienced an improved 4-year PFS compared to the other treatment arms (60% vs. 44%, prostate only RT (PORT) and NAHT; vs. 49%, WPRT and adjuvant hormonal therapy (AHT); vs. 50% PORT and AHT) (Roach et al. 2003). However, this difference diminished with longer follow-up. Even more odd, men who received WPRT and AHT fared the worst among the four subgroups (Lawton et al. 2007). Ultimately, the study was not powered for cross comparisons between the four treatment arms, thus allowing little room for interpretation of the actual value of WPRT. Around the same time, the French trialists' group reported the early 5-year results of GETUG-01, which just like the other preceding studies, also failed to justify WPRT (Pommier et al. 2007). It is also apparent that patient selection was inconsistent across the three trials. Although GETUG-01 comprised of mostly patients with NCCN-defined high-risk CaP (78.7%), only approximately half of the study cohort possessed a ≥15% risk of lymph node metastasis as estimated by the Roach's equation (48.7% and 43.2% in WPRT and PORT arms, respectively).

Retrospective series however offered a different perspective to the benefits of irradiating the pelvic lymph nodes (Seaward et al. 1998a, b; Pan et al. 2002; Jacob et al. 2005; Aizer et al. 2009; Milecki et al. 2009; Mantini et al. 2011). Seaward et al. retrospectively selected patients who were at risk of lymph node metastasis using the Roach's equation and demonstrated that these patients experienced an improved PFS if they received WPRT (Roach's score ≥ 15–35%, median PFS 39.5 months for WPRT vs. 22.5 months for PORT; >35%, 27.2 months vs. 20.8 months, respectively) (Seaward et al. 1998a, b). Pan et al. also presented similar findings using a different method of lymph node risk stratification (Partin's) (Partin et al. 2001; Pan et al. 2002). In that study, WPRT was only beneficial in individuals with an intermediate risk of lymph node metastasis, but not for low- and high-risk patients. Nonetheless, the main limitation of both studies relates to the fact that the majority of patients were not treated with concomitant androgen deprivation and RT.

A number of predictive models for lymph node metastasis have been developed (Partin et al. 1993;

Table 2 Overview of trials addressing the issue of pelvic nodal radiotherapy

Trial	Start	*N*	Inclusion criteria	Randomisation	Median follow-up	Main finding	Toxicity	Publication
RTOG 77-06 (Pre-PSA era)	1978	445	Stage A2 and B without clinical (lymphangiogram) or biopsy evidence of lymph node involvement	65 Gy in 1.8–2 Gy fractions to prostate alone vs. pelvic node irradiation to 45 Gy with a boost of 20 Gy to the prostate	7 and 12 years	7-year OS 80% vs. 78% RFS 88% vs. 90% MFS 84% vs. 83% NED 67% vs. 64% (all p = NS) 12-year OS difference (p = NS)	Not reported	Asbell et. al. 1988 Asbell et. al. 1998
RTOG 9413	1995	1,323	All T and all GS PSA < 100 ng/mL Risk of nodal involvement > 15%	70.2 Gy to the prostate alone vs. 50.4 Gy to the pelvis + 19.8 Gy boost to the prostate Neoadjuvant + concurrent + adjuvant HT vs. adjuvant HT	7 years	OS and PFS difference between WPRT and PORT group was NS	No difference in late GU grade ≥ 3 (p = 0.16) Late GI grade ≥ 3 5% (WPRT + NHT arm) vs. 1% (PORT + NHT) (p = 0.002)	Roach et. al. 2003 Lawton et. al. 2007

GETUG 01	1998	444	T1b–T3, N0 6 months of ADT allowed for HR patients	46 Gy to the pelvis followed by boost to the prostate to 66–70 Gy vs. 66–70 Gy to the prostate alone	3.5 years	5-year PFS 66% vs. 65.3% ($p = 0.34$)	Acute GU grade ≥ 3 was significantly higher in the prostate-only radiotherapy arm. Pelvic irradiation was associated with a small but NS increase in late GU grade ≥ 2	Pommier et. al. 2007
RTOG 0924 (active trial)	2011	Target accrual 2,580 Current accrual 1,068	GS 7–10 + T1c-T2b + PSA < 50 ng/ml GS 6 + T2c-T4 or ≥50% positive biopsies + PSA < 50 ng/ml GS 6 + T1c-T2b + PSA > 20 ng/ml	Neoadjuvant ADT + prostate and seminal vesicle RT (45 Gy) + boost to prostate and proximal seminal vesicles (IMRT 34.2 Gy or brachy) vs. Neoadjuvant ADT + whole-pelvic RT (45 Gy) + boost to prostate and proximal seminal vesicles (IMRT 34.2 Gy or brachy)	N/A	N/A	N/A	Recruitment ongoing

OS overall survival, *RFS* recurrence-free survival, *MFS* metastasis-free survival, *NED* no evidence of disease, *NS* not significant, *T* T stage, *PSA* prostate-specific antigen, *GS* Gleason score, *HT* hormonal therapy, *PFS* progression-free survival, *WPRT* whole pelvis radiotherapy, *PORT* prostate only radiotherapy, *NHT* neoadjuvant hormonal therapy, *ADT* androgen deprivation therapy, *HR* high risk

Roach et al. 1994; Nguyen et al. 2009; Briganti et al. 2012a, b). While most have been validated to some extent in large surgical series, Roach's equation is perhaps the most intuitive and routinely applied formula. It also outperforms other newly proposed models (Yu and Nguyen formulas) and remained valid in the extended pelvic lymph node dissection (ePLND) series (Abdollah et al. 2013). Based on data generated from ePLND series, it can be surmised that risks of pelvic lymph node metastasis are in the range of 5–6%, 20–25% and 30–40% for low- , intermediate- and high-risk CaP, respectively (Heidenreich et al. 2007). There is further suggestion that extent of lymph node dissection correlated with PCSM (Joslyn and Konety 2006). It is thus counter-intuitive if radiation oncologists avoid pelvic RT in patients with intermediate- and high-risk CaP. Perhaps, a way forward is to independently test the value of WPRT/ePLND in subgroups of CaP patients stratified according to their likelihood of nodal metastasis. Along similar principles, RTOG 0924 is a randomised phase III trial evaluating WPRT and androgen deprivation in patients with 'favourable' high-risk CaP (defined as GS 7–10, PSA < 50 ng/ml; GS 6, PSA < 50 ng/ml, cT2c-4; GS 6, PSA > 20 ng/ml, cT1c-2b) (Kattan et al. 2003).

6 Whole Pelvis Radiotherapy in Node-Positive Advanced Prostate Cancer

Conventional thinking among oncologists suggests that node-positive CaP is associated with adverse prognosis and is likely incurable. This is backed by robust observations in surgically treated cohorts that nodal metastasis was a strong determinant of distant metastasis and PCSM (Gerber et al. 1997; Cheng et al. 2001; Eggener et al. 2011). However, there is now emerging evidence that node-positive CaP represents a heterogeneous subgroup, with a substantial proportion of men capable of experiencing long-term bRFR and survival with aggressive treatment (Cheng et al. 2001; Swanson et al. 2006; Briganti et al. 2009; von Bodman et al. 2010; Carlsson et al. 2013; Touijer et al. 2014; Abdollah et al. 2014). Consistent in all the published reports, the number of involved nodes is a significant prognostic determinant, independent of other clinical indices like GS, PSA and cT category. Men who have limited nodal metastases of ≤2 nodes are less likely to fail biochemically, develop distant metastasis and encounter PCSM (Cheng et al. 2001; von Bodman et al. 2010; Touijer et al. 2014). In fact, 75–86% of 10-/15-year cancer-specific survival rates post-RadP and ePLND have been reported in patients with ≤2 pathologically involved lymph nodes (Boorjian et al. 2007; Briganti et al. 2008; Schumacher et al. 2008; Touijer et al. 2014; Gakis et al. 2014). Going a step further, long-term survival has been reported in men with node-positive CaP managed by RadP and PLND alone, despite evidence presented by Messing et al. favouring immediate over delayed androgen deprivation in this group of men (Messing et al. 2006; Schumacher et al. 2008; Touijer et al. 2014). Collectively, these findings argue for the role of aggressive treatment in carefully selected men with node-positive CaP. In support, three surgical series, including a series by Engel et al. comprising of 957 patients, have independently reported a two-fold PFS benefit with combined local and hormonal treatment than with hormonal treatment alone (Engel et al. 2010; Grimm et al. 2002; Steuber et al. 2011).

Likewise, there is also emerging evidence demonstrating the efficacy of RT in node-positive CaP. Based on data queried from the National Cancer Data Base (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) database, Tward et al. and Rusthoven et al. have independently reported PCSM and OS benefits with offering RT to these high-risk patients (Tward et al. 2013; Rusthoven et al. 2014). Tward et al. reported an HR of 0.66 for PCSM with pelvic RT in their analysis of 1,100 patients, while Rusthoven et al. demonstrated an absolute benefit of 20% for OS with either RadP or RT. A similar degree of benefit was also observed with combined modality treatment as opposed to hormonal therapy alone in the subgroup of men with pathologically proven node-positive CaP from RTOG 85-31 (Lawton et al. 2005). RTOG 96-08 (a phase III trial of total androgen suppression vs. total androgen suppression plus definitive external beam irradiation for pathologic lymph node-positive adenocarcinoma of the prostate) closed

prematurely due to poor accrual, but, nonetheless, reported a 20% benefit in 10-year OS in men who received combination treatment (46% vs. 67%) (Zagars et al. 2001). Two other more recent analyses, namely, an exploratory analysis of the STAMPEDE trial (NCT00268476; MRC PR08; CRUK/06/019) and a retrospective review of 3,682 NCDB records of men with node-positive CaP by Lin et al., also indicated better failure-free survival (HR = 0.45) and OS (24.4% absolute improvement) with the addition of local treatment (James et al. 2015a, b; Lin et al. 2015).

Overall, there is sound non-level 1 evidence to support the argument that pelvic RT should be offered to patients with node-positive CaP. Nonetheless, unresolved issues in this regard include target and dose definitions for RT planning and patient selection. There are now consensuses on the coverage of pelvic nodal chains for clinical target volume contouring (Taylor et al. 2007; Lawton et al. 2009). Although there is uncertainty regarding the optimal dose to gross nodal metastasis, high tumouricidal doses (≥70 Gy) to sites in the pelvis that historically would have been unachievable using 3D conformal RT are now possible with IMRT and IGRT. Separately, we lack an optimal criterion for recommending pelvic RT to patients with node-positive disease. To this end, Abdollah et al. recently published a novel PCSM-risk stratification model based on 1,107 patients with pathologically positive nodes who underwent RadP, ePLND and androgen deprivation with or without pelvic RT (Abdollah et al. 2014). They determined that two categories of men with node-positive CaP were likely to benefit from adjuvant RT: (1) ≤2 positive nodes, GS 7–10 and pT3b/4 or positive surgical margins and (2) 3–4 positive nodes. This represents the first of its kind clinical decision-making tool and should certainly be validated prospectively.

7 Oligometastatic Prostate Cancer: Radiotherapy for Palliation or Cure?

The concept of 'curing' patients with oligometastatic disease across all tumour types has gained popularity once again in recent times. While the evidence in support of a 'curable' oligometastatic state is more abundant in some cancer types like colorectal cancer, renal cell carcinoma and sarcomas, it is conceivable that a subset of patients with metastatic CaP can be 'cured' with aggressive treatment. Current methods of stratifying for these favourable patients are imprecise and do not incorporate indices indicative of tumour biology. For the lack of a better measure, patients with metastatic CaP are often crudely stratified based on (1) number of extra-pelvic lesions, (2) whether these metastatic tumour sites are amendable to ablative therapies (surgery or SBRT), and (3) the magnitude of PSA response following initial androgen deprivation. In truth, it is not yet known if patients harbouring these characteristics indeed have a better prognosis, but a few retrospective reviews have suggested a benefit in disease control with aggressive therapy. For example, Culp et al. reviewed 374 men with metastatic CaP from the SEER database who underwent RadP or brachytherapy and reported better OS and failure-free survival for individuals who underwent local treatment compared to those who did not (Culp et al. 2014). In another report of 119 patients who were treated with SBRT to isolated nodal or skeletal metastasis, 3-year progression-free rate was 31%, with corresponding 95% of 3-year and 88% of 5-year OS in that cohort (Ost et al. 2016). Although these results may seem promising at first glance, several questions still exist on the clinical management of this patient subgroup.

Foremost, the ideal clinical endpoint that constitutes a robust surrogate for the assessment of treatment efficacy is unclear. In this instance, suitable choices include clinical PFS, OS, time to salvage hormonal therapy or time to castrate resistance. Perhaps, for the purpose of a clinical trial, it may be prudent to select an endpoint that is both measurable at an early time-point and also functions as a good surrogate for long-term outcome, especially since a substantial proportion of patients with metastatic CaP treated in the docetaxel era do survive beyond 5 years (James et al. 2015a, b). Secondly, much work is needed in defining the optimal treatment schema. Uncertainties pertaining to (1) timing of RT post-initial androgen deprivation, (2) RT doses to the prostate and metastatic lesions, (3) duration of androgen deprivation (2–3 years vs. continuous lifelong) and (4) combination strategies

with docetaxel ought to be examined. Hopefully, an ongoing Canadian prospective trial (ClinicalTrials.gov; NCT02563691) will provide answers to some of these conundrums. Thirdly, through multiregion deep whole genome sequencing of multifocal primary and recurrent CaP, we now have a deeper understanding of the clonal dynamics and divergent evolutionary processes driving the progression to lethal CaP (Hong et al. 2015; Gundem et al. 2015). We need to learn how best to incorporate biological and clinical indices to enable better patient stratification, so that we truly select for the 'curable' oligometastatic CaP patients. Research across these domains is desperately needed, but meanwhile the treatment paradigm of metastatic CaP continues to evolve rapidly.

8 Adjuvant Radiotherapy or Salvage Only at Biochemical Failure Post-Radical Prostatectomy?

It is estimated that following RadP, approximately 30–60% of men will require RT as salvage for biochemical failure (Pfister et al. 2014). Likelihood of salvage is dependent on clinical indices, such as pre-RT PSA, GS, surgical margin status and PSA doubling time (Stephenson et al. 2007). Individually, these parameters are indicative of tumour burden, biology and likelihood of local vs. distant recurrences.

While there is cognition of RT as an effective salvage measure for biochemical relapse post-RadP, the timing of treatment is debatable. The argument for offering RT immediately post-RadP in a select group of high-risk patients (pT3/4 and/or with positive surgical margin) relates closely to the correlation between tumour control probability (TCP) and microscopic tumour burden. Three randomised trials were performed to test this hypothesis. Overview of these landmark trials is presented in Table 3. SWOG 8794 was the first conducted between 1988 and 1997 recruiting 425 CaP patients harbouring such features. Updated results after a median follow-up of 12 years revealed that men who received adjuvant RT experienced a lower incidence of distant metastases compared to those who were observed (9.3% vs. 17.5%, respectively; HR = 0.71 [0.54–0.94]) (Thompson et al. 2009). OS, bRFR and dependence on salvage hormonal therapy also favoured adjuvant RT (Thompson et al. 2006). EORTC 22911 studied the role of adjuvant RT in 1,005 men and reported a 50% relative reduction in 10-year risks of biochemical and local relapses (Bolla et al. 2005, 2012). Incidences of distant failures however did not differ between treatment arms in EORTC 22911. To note, incidence of distant metastasis was also significantly lower in EORTC 22911 relative to SWOG 8794 (7.2% vs. 17.5%). This discrepancy is unexplained by differences in clinical characteristics between the studies (higher proportion of pT3b, but lower GS tumours in SWOG 8794 than EORTC 22911). Last but not least, the German study group (ARO 96-02) showed, like the other two studies, a relative reduction of 50% in biochemical recurrence with adjuvant RT in patients who achieved an undetectable PSA post-RadP (about a third of patients had a PSA of >0.2 ng/ml post-RadP in SWOG 8794 and EORTC 22911) (Wiegel et al. 2009, 2014). Again, no benefit in terms of distant metastasis control and OS was observed in ARO 96-02.

Perhaps, the inter-study variation for incidences of distant metastasis (13.4% of SWOG 8794 vs. 7.2% of EORTC 22911 vs. 15.3% of ARO 96-02) highlights the fact that clinical indices alone are imprecise for prediction of lethal disease in the adjuvant setting. In this regard, genomic indices could be a powerful tool (Antonarakis et al. 2012; Viers et al. 2014; Den et al. 2014; Evans et al. 2016). Using a novel RNA-based genomic classifier, Den et al. were able to stratify for patients at risk of rapid failures post-RadP and would benefit from early rather than late RT, potentially providing the first biomarker as a clinical decision-making tool for timing of RT post-RadP (Den et al. 2015). Evans et al. also demonstrated the prognostic utility of a DNA damage and repair pathway-based gene expression signature for distant metastasis post-RadP in a large sample size of 1,090 men, validated by multi-cohort testing (Evans et al. 2016). Separately, the indolent nature of CaP also

Table 3 Basic characteristics of landmark adjuvant radiotherapy trials

Trial	Start	*N*	Inclusion criteria	RT dose	PSA at trial entry	Median follow-up	Definition of PSA failure	Main finding	Toxicity	Publication
SWOG 8794	1988	425	pT3 or R1	60–64 Gy to the prostate bed	≥0.2 ng/mL: 33% <0.2 ng/mL: 66%	10.6 years	PSA > 0.4 ng/mL	MFS 12.9 years vs. 14.7 years for observation vs. ART ($p = 0.016$) OS 13.3 years vs. 15.2 years for observation vs ART ($p = 0.0023$)	Proctitis 3.3% vs. 0% Urethral strictures 17.8% vs. 9.5% Urinary incontinence 6.% vs. 2.8% (ART vs. observation)	Thompson et. al. 2006 Thompson et. al. 2009
EORTC 22911	1992	1,005	pT2-3 and/or R1	60 Gy to the prostate bed	>0.2 ng/mL: 30% ≤0.2 ng/mL: 70%	10.6 years	Increase in PSA > 0.2 µg/L over the lowest post-op value	10-year BPFS 61% vs. 41% for ART vs. observation ($p < 0{\cdot}0001$)	10-year incidence - all grade 3 5.3% vs. 2.5% GU grade 2 21.3% vs. 13.5% GI grade 2 2.5% vs. 1.9% (ART vs. observation)	Bolla et. al. 2005 Bolla et. al. 2012
ARO 96-02	1996	388	pT3-4 ± R1	60 Gy	Undetectable	10 years	Two increasing PSA readings	10-year PFS 56% vs. 35% (ART vs. WS) ($p < 0.0001$)	Grade 3 bladder toxicity 1% vs. 0% (ART vs. WS)	Wiegel et. al. 2009 Wiegel et. al. 2014

SWOG Southwest Oncology Group, *PSA* prostate-specific antigen, *R1* positive margins, *MFS* metastasis-free survival, *ART* adjuvant radiotherapy, *OS* overall survival, *EORTC* European Organisation for Research and Treatment of Cancer, *BPFS* biochemical progression-free survival, *GU* genitourinary, *GI* gastrointestinal, *PFS* progression-free survival, *WS* wait and see

implies that time from biochemical progression to clinical disease is often protracted. In a large-scale analysis of 1997 men who underwent RadP, median time taken to develop distant metastasis from the point of biochemical failure was 8 years (Pound et al. 1999). If so, 10 years of follow-up may be inadequate for the assessment of distant metastasis-related outcomes in adjuvant vs. salvage RT trials.

In light of the results of SWOG 8794, EORTC 22911 and ARO 96-02, adjuvant RT is currently jointly endorsed by ASTRO, AUA and ASCO in patients with (1) extensive pT3a or pT3b and (2) GS 8–10 and (3) those who failed to achieve post-operative PSA nadir (Valicenti et al. 2013; Freedland et al. 2014).

In spite of this, a recent nationwide survey revealed continuous declining use of post-operative RT in CaP from 2005 to 2011 in the United States (Sineshaw et al. 2015). Arguments for this trend include; first, SWOG 8794 and EORTC 22911 had failed to incorporate undetectable PSA as an inclusion criterion, and therefore it is often argued that these patients were at a significantly higher risk of progression and mortality at the outset (Wiegel et al. 2015). Secondly, a subsequent central pathology review of the EORTC 22911 cohort suggested that only patients with positive margins derived a benefit from adjuvant RT (van der Kwast et al. 2007). Thirdly, up to 50% of patients who experienced biochemical failure are salvaged successfully if RT is initiated early enough, as indicated by several large retrospective studies (Trock et al. 2008; Stephenson et al. 2007; Briganti et al. 2012a, b; Pfister et al. 2014). Finally, adjuvant RT is not without increased toxicities (increased incidence of urethral strictures and urinary incontinence) (Bolla et al. 2005; Thompson et al. 2006; Wiegel et al. 2009; Iyengar et al. 2011). Given the ongoing controversy regarding the preferred management of patients with high-risk features on RadP, three large randomised trials, namely, RADICALS (Radiotherapy and Combined Androgen Deprivation after Local Surgery), RAVES (Radiotherapy Adjuvant vs. Early Salvage following Radical Prostatectomy) and GETUG 17 aimed to resolve the issue of timing of RT post-RadP (Parker et al. 2007; Pearse et al. 2014) (Table 4). Primary endpoints of these studies are PCSM, bRFR and event-free survival, respectively. Results of these studies are expected in 2016.

9 Prevailing Controversy of the α/β of Prostate Cancer

Alpha-beta ratio (α/β) is a parameter indicative of tissue fraction size sensitivity and is estimated through the linear quadratic (LQ) equation. Briefly, tissues with low α/β are more sensitive to fraction size changes, and this intrinsic characteristic bears therapeutic implications in terms of designing optimal RT fractionation schemes. In CaP, since the seminal publication by Brenner et al., several subsequent analyses have independently concluded a low α/β ratio (range of 1.2–4.1) for CaP, thus setting the stage for several studies testing a variety of novel hypofractionation schemes (Brenner and Hall 1999; Miralbell et al. 2012; Dasu and Toma-Dasu 2012; Vogelius and Bentzen 2013).

However, despite hypotheses of better outcomes with these hypofractionation schemes that were formulated on the backbone of LQ modelling, evidence so far points only to non-inferiority of hypofractionated RT when compared to conventional RT. Table 5 provides an overview of the results of landmark randomised studies that compared conventional RT against moderately hypofractionated RT schedules (dose/fraction ranging from 2.4 to 3.1 Gy). Early hypofractionation studies by Yeoh et al. and Lukka et al. may have reported better bRFR with hypofractionated treatment schemes, but in truth, the RT doses for the conventional arms were low by contemporary standards (Yeoh et al. 2011; Lukka et al. 2005). Five other large randomised trials, namely, CHHiP, NRG RTOG 0415, Fox Chase Cancer Centre study, Italian study and MD Anderson Cancer Centre study, employed dose-escalated conventional treatment schemes, and early results did not suggest differences in tumour control and toxicities with hypofractionated RT (Dearnaley

Table 4 Ongoing randomised trials comparing adjuvant versus salvage radiotherapy addressing the question of timing of radiotherapy post-radical prostatectomy

Trial	Start	Inclusion criteria	Definition of post-op PSA failure	Randomisation	RT dose	RT volume	ADT	Primary endpoint	Planned accrual
RADICALS (MRC/NCIC) NCT00541047	2007	Post-op PSA ≤0.2 ng/ml and/or pT3/4, GS 7–10, pre-op PSA ≥ 10 ng/ml, R1	Two consecutive rises in PSA and final PSA >0.1 ng/ml or three consecutive rises in PSA	Immediate RT (within 26 weeks after RadP) vs. deferred RT at BF	66 Gy in 33 fr or 52.5 Gy in 20 fr to the prostate bed 46 Gy in 23 fr to the pelvic lymph nodes	Prostate bed ± pelvic lymph nodes	LHRH agonist or bicalutamide 150 mg Randomisation No ADT vs. 6 months vs. 2 years of ADT	DSS	closed; 2840 patients randomized in hormone duration question and 1396 patients randomized in radiotherapy timing question
RAVES (TROG 08.03) NCT00860652	2009	Post-op PSA ≤ 0.1 ng/mL R1, EPE ± pT3b	PSA ≥ 0.2 ng/ml	Adjuvant RT (within 4 months after RadP) vs. early salvage	64 Gy in 32 fr	Prostate bed	Not allowed	BF (PSA ≥0.4 ng/ml)	470 (closed)
GETUG 17 NCT00667069	2007	Post-op PSA ≤ 0.1 ng/mL pT3/4 or R1	PSA > 0.2 ng/ml	Immediate (within 6 months after RadP) vs. delayed RT	66 Gy in 33 fr to the prostate bed 46 Gy in 23 fr to the pelvic lymph nodes	Prostate bed ± pelvic lymph nodes	Triptorelin 6 months	EFS at 5 years	718 (ongoing)

ADT androgen deprivation therapy, *PSA* prostate-specific antigen, *R1* positive margins, *RT* radiotherapy, *RadP* radical prostatectomy, *BF* biochemical failure, *fr* fractions, *GS* Gleason score, *LHRH* luteinising hormone-releasing hormone, *DSS* disease-specific survival, *EPE* extra-prostatic extension *BF* biochemical failure, *EFS* event-free survival

Table 5 Summary of main randomised trials looking at hypofractionated radiotherapy

Trial	*N*	Median follow-up	RT schedule	Gy per fraction	BED (Gy)			Primary outcome	Secondary outcome	Late toxicity	Reference
					α/β = 1.5 (prostate cancer)	α/β = 3 (normal tissue)	α/β = 10 (tumor)				
Australian trial	217	7.5 years	64 Gy/32 fr	2 Gy	149	107	77	7.5-year BRFS 34% ($p < 0.05$)	7.5-year OS 69% (p = NS)	No significant difference	Yeoh et. al. 2006 Yeoh et. al. 2011
			55 Gy/20 fr	2.75 Gy	156	105	70	7.5-year BRFS 53% ($p < 0.05$)	7.5-year OS 71% (p = NS)		
Ontario (Canada)	936	5.7 years	66 Gy/33 fr	2 Gy	154	110	79	5-year BCF 52.95%	5-year OS 85% (p = NS) 2-year PBR 53% (p = NS)	No significant difference	Lukka et. al. 2005
			52.5 Gy/20 fr	2.63 Gy	145	98	66	5-year BCF 59.95%	5-year OS 87% (p = NS) 2-year PBR 51% (p = NS)		
CHHiP (CRUK/06/016)	3,216	5.2 years	60 Gy/20 fr	3 Gy	180	120	78	5-year FFBF 90.6%	Not reported	2-year grade ≥ 2 late GU 1.7% (p = 0.34) 2-year grade ≥ 2 late GI 2.9% (p = 0.1)	Dearnaley et. al. 2016
			57 Gy/19 fr	3 Gy	171	114	74	5-year FFBF 85.9% (p = 0.003)		2-year grade ≥ 2 late GU 1.1% (p = 0.34) 2-year grade ≥ 2 late GI 1.8% (p = 0.1)	
			74 Gy/37 fr	2 Gy	173	123	89	5-year FFBF 88.3%		Not reported	

Trial	*N*	Median follow-up	RT schedule	Gy per fraction	BED (Gy)			Primary outcome	Secondary outcome	Late toxicity	Reference
					α/β = 1.5 (prostate cancer)	α/β = 3 (normal tissue)	α/β = 10 (tumor)				
NRG Oncology RTOG 0415	1,115	5.9 years	73.8 Gy/41 fr	1.8 Gy	162	118	87	7-year DFS 75.6% (p = NS)	FFBF and OS not different	Grade ≥ 3 GI 3% grade ≥ 3 GU 4.5% (both p = NS)	Lee et. al. 2016
			70 Gy/28 fr	2.5 Gy	187	128	88	7-year DFS 81.8% (p = NS)		Grade ≥ 3 GI 4.6% grade ≥ 3 GU 6.4% (both p = NS)	
Fox Chase Cancer Center	303	5.7 years	76 Gy/38 fr	2 Gy	177	127	91	5-year BCDFR 21.4% (p = 0.7)	PCD and OS not different	Grade 3 late GU 3.3% (p = NS) Grade 3 late GI 2% (p = NS)	Pollack et. al. 2013
			70.2 Gy/26 fr	2.7 Gy	197	133	89	5-year BCDFR 23.3% (p = 0.7)		Grade 3 late GU 4% (p = NS) Grade 3 late GI 2% (p = NS)	
Italian	168	5.8 years	80 Gy/40 fr	2 Gy	187	133	96	5-year BFFS 79% (p = 0.065)	5-year FFLF 91% (p = 0.33) 5-year FFDF 86% (p = 0.29) 5-year CSS 82% (p = 0.16) 5-year OS 92% (p = 0.13)	3-year grade ≥ 2 GU 11% 3-year grade ≥ 2 GI 16% (both p = NS)	Arcangeli et. al. 2010, 2012
			62 Gy/20 fr	3.1 Gy	190	126	81	5-year BFFS 85% (p = 0.065)	5-year FFLF 93% (p = 0.33) 5-year FFDF 90% (p = 0.29) 5-year CSS 92% (p = 0.16) 5-year OS 98% (p = 0.13)	3-year grade ≥ 2 GU 14% 3-year grade ≥ 2 GI 17% (both p = NS)	

(continued)

Table 5 (continued)

Trial	*N*	Median follow-up	RT schedule	Gy per fraction	BED (Gy)			Primary outcome	Secondary outcome	Late toxicity	Reference
					α/β = 1.5 (prostate cancer)	α/β = 3 (normal tissue)	α/β = 10 (tumor)				
MDACC	204	5 years	72 Gy/30 fr	2.4 Gy	187	130	89	5-year PSAFFS 96% (p = NS)	Not reported	5-year grade ≥ 2 GU 15.8% (p = 0.97) 3-year grade ≥ 2 GI 10% (p = 0.11)	Kuban et. al. 2008 Hoffman et. al. 2014
			75.6 Gy/42 fr	1.8 Gy	166	121	89	5-year PSAFFS 92% (p = NS)		3-year grade ≥ 2 GU 16.5% (p = 0.97) 3-year grade ≥ 2 GI 5.1% (p = 0.11)	

BED biological equivalent dose, *BRFS* biochemical relapse-free survival, *OS* overall survival, *BCF* biochemical/clinical failure, *PBR* positive biopsy rate, *CRUK* Cancer Research UK, *FFBF* freedom from biochemical failure, *GU* genitourinary, *GI* gastrointestinal, *DFS* disease-free survival, *PCD* prostate cancer death, *OS* overall survival, *NS* not significant, *BCDFR* biochemical and/or clinical disease failure, *BFFS* biochemical failure-free survival, *FFLF* freedom from local failure, *FFDF* freedom from distant failure, *CSS* cancer-specific survival, *MDACC* MD Anderson Cancer Center, *PSAFFS* PSA failure-free survival

et al. 2016; Robert Lee et al. 2016; Pollack et al. 2013; Arcangeli et al. 2012; Kuban et al. 2008). In particular, the fact that bRFR did not differ between treatment arms, despite the design of a more 'biologically effective' RT regime, queries the reliability of the α/β ratio that was applied in some of these studies. For example, in Fox Chase Cancer Centre study by Pollack et al., the experimental hypofractionation arm was estimated to equate to 84.4 Gy in 2 Gy fraction size based on the assumption of an α/β ratio of 1.5 Gy, but yet, no dose-response was observed with the 8.4 Gy dose increment (Pollack et al. 2013). Meanwhile, we await results of two other trials of moderate hypofractionation, namely, the Dutch HYPRO trial of 78 Gy vs. 64.6 Gy in 2 and 3.4 Gy fraction sizes, respectively, and the Ontario PROFIT trial of 78 Gy vs. 60 Gy in 2 and 3 Gy fraction sizes, respectively (Aluwini et al. 2015). With the collection of prospective evidence, it is certain that updated TCP/LQ modelling will yield more robust estimates of the true α/β ratio of CaP.

Taking a step further, studies on extreme hypofractionation have also been conducted in CaP and are gaining popularity in the several parts of the world. Typically, extreme hypofractionation entails a 5-fraction regime with the delivery of 7–7.25 Gy per session using SBRT techniques. There are however concerns that prostate SBRT is associated with an increase of clinically significant urinary and gastrointestinal toxicities (Yu et al. 2014; Kim et al. 2014). Thus, until the preliminary toxicity data of prospective studies becomes available, including the international multicentre PACE trial (Prostate Advances in Comparative Evidence, NCT01584258), this form of treatment should not be routinely offered to patients.

10 The Future of Proton Radiotherapy in the Treatment of Prostate Cancer

Interest in proton particle RT arose from the unique physical characteristics of protons upon tissue interaction. The Bragg's peak, a property associated with particle therapy, describes the deposition of energy at a specific tissue depth with minimal entering and exit doses. The resultant effect is reduced doses to adjacent normal tissues.

The only currently available randomised evidence for the efficacy of proton RT in CaP comes from the Massachusetts General Hospital dose-escalation trial (RTOG 95-09), where study investigators examined the benefits of an escalated boost dose that was delivered using proton RT. Despite a high dose of 79.2 Gy (boost of 28.8 Gy), only 2% and 1% of the cohort experienced late grade ≥ 3 genitourinary and gastrointestinal toxicities, respectively (Zietman et al. 2010). Other studies reporting on comparative effectiveness and patient-reported quality of life outcomes between proton RT and other modalities have been mostly single-institution prospective series (Sheets et al. 2012; Gray et al. 2013; Hoppe et al. 2014; Mendenhall et al. 2014). With limited follow-up, it is preliminary to judge if dosimetric superiority and theoretical advantages of proton RT yield tangible therapeutic benefits, but so far, there appears to be no obvious difference between proton RT and more contemporary techniques of photon RT.

The controversy of utilising proton RT for treating CaP is compounded by the high cost associated with developing these centres (Lawrence and Feng 2013). It is unsurprising then that market-oriented strategies had specifically targeted CaP patients, as opposed to other perhaps more pertinent indications such as brain and eye tumours in children, for the sake of securing financial viability. However, insurance companies have progressively declined to reimburse inflated prices for proton RT in patients with CaP, given the lack of compelling data for a therapeutic advantage. It is thus imperative that the oncology community remained committed to generate sound evidence, preferably from randomised studies, so as to inform on the clinical utility of proton RT in the treatment of CaP (Bekelman and Hahn 2014). To this end, a multi-institutional randomised trial (PARTIQoL, Clinicaltrials.gov, NCT01617161), jointly sponsored by the National Cancer Institute and Massachusetts General Hospital, is currently

underway to compare IMRT and proton RT in the treatment of organ-confined CaP.

Conclusion

The modern practice of IMRT/IGRT in treating CaP has certainly come a long way from less than ideal 3D conformal RT, with patients now enjoying better than ever cure rates and quality of life outcomes due to unparalleled precision in targeting the prostate gland. Having said, judging from the wide-ranging topics that were discussed in this chapter, it is apparent that beyond technology, much work is needed to resolve issues relating to optimal clinical management of CaP. Broadly, they encompassed (1) improving the manner of patient stratification, (2) avoiding unnecessary treatment in patients with favourable prognosis, (3) optimising intensive treatment in patients with unfavourable intermediate-/high-risk/oligometastatic disease and (4) progressive incorporation of technology with biology to achieve greater 'physical' and 'biological' precision in the targeting of CaP. Addressing these issues entails a multidisciplinary approach involving urologists, radiation and medical oncologists and internists; all invested in the endeavour with the sole committed objective of improving the outcomes of patients with CaP.

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