Summary of Ongoing Prospective Trials Using SBRT for Prostate Cancer

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Kirsty Morrison and Nicholas van As

Evidence is building to support the use of stereotactic radiotherapy in the management of localised prostate cancer. However, a large number of uncertainties remain, highlighting the need for further prospective trials. This chapter will consider ongoing prospective trials which may influence the future of SBRT in localised prostate cancer. Eighty two trials have been identified following a search of http://clinicaltrials.gov and www.isrctn.com most recently performed in December 2017, using search terms: prostate SBRT; prostate stereotactic; prostate hypofractionation; prostate CyberKnife; prostate focal radiotherapy; and prostate dominant lesion. Trials investigating SBRT for reirradiation or in the preoperative or salvage radiotherapy setting have been excluded, and are not discussed within the scope of this chapter. The larger/most relevant remaining trials are summarised in Tables 14.1, 14.2 and 14.3.

14.1 SBRT in Low- and Intermediate-Risk Prostate Cancer

There is now a wealth of published data from non-randomised studies demonstrating the efficacy and safety of SBRT in low- and

intermediate-risk prostate cancer, to be consistent with standard treatment modalities. However, many of these studies are retrospective in nature, and often with short follow up at the time of publication, making it difficult to draw accurate conclusions. Ongoing prospective trials therefore remain vital in this setting. There are a large number of ongoing non-randomised trials evaluating SBRT as monotherapy for low- and intermediate-risk patients. The majority of these are single-arm studies, delivering SBRT in five fractions most commonly at a prescribed uniform dose of 36.25 Gy (range 35–40 Gy) to the PTV. The larger of these studies with an expected accrual of at least 50 patients, are summarised in Table 14.1. Other trials evaluating the use of dose escalation and more extreme hypofractionation will be discussed later in this chapter.

In terms of multicentre trials, the phase II trial by Meier et al. [21] has completed accrual and has recently published 5 year outcomes in abstract form [22]. Over 300 low- and intermediate-risk patients were treated using CyberKnife with a prescription dose of 36.25 Gy in five fractions, aiming to deliver 40 Gy to the prostate. Results were encouraging demonstrating biochemical progression-free survival (bPFS) of 97.1% and low toxicity rates with no grade 3 gastrointestinal (GI) and 2% late genitourinary (GU) toxicity. Within the SMART trial [24] linac-based techniques were used, delivering a dose of 37 Gy in five fractions prescribed to the PTV. Results

K. Morrison (✉) · N. van As
Royal Marsden Hospital, London, UK
e-mail: kirsty.morrison@rmh.nhs.uk; Nicholas.vanas@rmh.nhs.uk

Table 14.1 Randomised SBRT trials

Centre/PI	Year open	Study design	Target accrual	Risk group	Arm 1/Experimental arm	Arm 2/Control arm	Primary objective	Status
PACE, van As (UK) [1]	2012	Multicentre Phase III	1092	L/I	SBRT 36.25 Gy/5 # to PTV CK/Linac	PACE A: Radical prostatectomy PACE B: EBRT 62 Gy/20 # or 78 Gy/39 #	PACE A: QOL 2 years PACE B: bPFS 5 years	PACE B: Active PACE A: Recruiting
RTOG0938, Lukka (CA) [2]	2011	Multicentre Phase II	255	L	SBRT 36.25 Gy/5 # twice weekly	EBRT 51.6 Gy/12 # consecutive days	QOL 1 year	Active Results [3]
HEAT, Abramowitz (US) [4]	2013	Multicentre	456	L/I	SBRT 36.25 Gy/5 #	EBRT 70.2 Gy/26 #	bPFS 2 years	Recruiting
Ellis (US) [5]	2018	Phase III	606	L/I	SBRT 5 # (alt days). Dose NS	EBRT 28 # 5 days/week. Dose NS	Toxicity/QOL 2 years	Not yet recruiting
Poon (HK) [6]	2015	Single centre Phase II	68	L/I	SBRT 36.25 Gy in 5 # twice weekly	EBRT 78 Gy in 39 #	QOL at 1 year	Recruiting
HYPO, Widmark (SE) [7]	2005	Multicentre Phase III	1200	I	EBRT 42.7 Gy in 7 #	EBRT 78 Gy in 29 #	FFBF 5 years	Active
Vuolukka (FI) [8]	2013	Single centre	44	L/I	SBRT 36.25 Gy in 5 # (alt days)	LDR brachytherapy (I125 seeds)	Toxicity 6 months	Active
Lukka (CA) [9]	2015	Single centre	40	L/I	SBRT with CyberKnife 36.25 Gy in 5 #	SBRT with VMAT 36.25 Gy in 5#	Patient acceptability	Unknown
PATRIOT, Ong, Loblaw (CA) [10]	2012	Multicentre Phase II	152	L/I	SBRT (Linac) 40 Gy in 5 # over 11 days	SBRT (Linac) 40 Gy in 5 # over 29 days	Bowel related QOL at 3 months	Active Results [11]
PROSINT, Greco (Portugal) [12]	2015	Single centre Phase II	30	L/I	SBRT 24 Gy in a single # VMAT/urethral sparing	SBRT 45 Gy in 5 # over 5 days VMAT/urethral sparing	Toxicity 5 years	Recruiting
Zelefsky (US) [13]	2017	Multicentre Phase III	200	I	SBRT 40 Gy in 5 # with Degarelix	SBRT 40 Gy in 5 # without hormones	Positive biopsy rate 2 years	Recruiting
Kang (US) [14]	2016	Single centre	40	L/I/H	SBRT 36.25 Gy in 5 # 2–3 times/week with endorectal balloon immobilisation	SBRT 36.25 Gy in 5 # 2–3 times/week with injectable rectal spacer	Toxicity 4 years	Recruiting

ASSERT Alexander/Kwan (CA) [15]	2016	Multicentre Phase II	80	I/H	SBRT 36.25 Gy/5 # weekly Linac/CBCT and fiducials 6–18 months ADT	EBRT 73.68 Gy/28 # 6–18 months ADT	Toxicity 5 years	Recruiting
Miralbell (CH) [16]	2012	Multicentre Phase II	170	L/I/H	SBRT 36.25 Gy in 5# over 9 days VMAT/urethral sparing (32.5 Gy) ADT in higher risk	36.25 Gy weekly over 28 days VMAT/urethral sparing (32.5 Gy) ADT in higher risk	Toxicity 5 years	Active
SPORT, Jain (UK) [17]	2016	Single centre	30	H	SBRT 36.25 Gy/5 # prostate and 25 Gy/5 # pelvis SBRT	SBRT 36.25 Gy in 5 # prostate alone	Feasibility Acute toxicity/ QOL	Recruiting
Suwinski (PL) [18]	2013	Phase III	350	I/H	SBRT or brachytherapy boost 10 Gy/ 2# following EBRT 76–78 Gy/38–39 #	EBRT 76–78 Gy/38–39 # alone	FFBF 3 years	Not yet open
HYPOPROST, Milecki (PL) [19]	2011	Multicentre	465	H	IMRT 46 Gy in 23 # prostate/pelvis and 30 Gy in 15 # prostate boost ADT up to 24 months	IMRT 46 Gy in 23 # prostate/pelvis and SBRT 15 Gy in 2 # prostate boost ADT up to 24 months	bPFS at 5 years	Recruiting
BLaStM Pollack (US) [20]	2015	Single centre Phase II	164	L/I/H	12–14 Gy in 1 # MRI guided SBRT boost then EBRT 76 Gy in 38 # ADT discretion of clinician	EBRT 76 Gy in 38 # and 91.2 Gy in 38 # SIB ADT discretion of clinician	Pathologic complete response 2–2.5 years	Recruiting

L low-risk, *I* intermediate-risk, *H* high-risk, *SBRT* stereotactic body radiotherapy, *Linac* Linear accelerator, *EBRT* external beam radiotherapy, *LDR* low-dose rate, *#* fractions, *VMAT* volumetric arc therapy, *CBCT* cone beam computerised tomography, *ADT* androgen deprivation therapy, *IMRT* intensity-modulated radiotherapy, *SIB* simultaneous integrated boost, *QOL* quality of life, *bPFS* biochemical progression-free survival, *FFBF* freedom from biochemical failure

Table 14.2 Non-randomised trials in low and intermediate risk prostate cancer

Centre/PI	Year open	Study design	Target accrual	Technique	Schedule	Primary objective	Status
Meier (US) [21]	2007	Multicentre Phase II	298	CK Fiducials	40 Gy/5 # to prostate 36.25 Gy/5 # to proximal SV	Toxicity bDFS 10 years	Active Results [22, 23]
SMART, Lee (US) [24]	2009	Multicentre Phase II	60	Linac Calypso or Exactrac and/or CBCT and fiducials	37 Gy/5 # to PTV (alt days)	Toxicity 3 years	Active Results [25]
Spratt (US) [26]	2011	Multicentre Phase II	66	Linac Calypso	37 Gy/5 # (alt days)	Quality of life 2 years	Completed Results [27]
Florida Robotic Radiosurgery Association, Perman (US) [28]	2010	Multicentre Observational	3000	NS	NS	Overall Survival 5 years	Recruiting
Tran (US) [29]	2013	Multicentre Phase I/II	105	NS	36.25 Gy/5 # (alt days)	Biochemical failure free rate 5 years	Active
HYPOSTAT, Dunst (DE) [30, 31]	2015	Multicentre Phase II	85	CK Fiducials	35 Gy/5 # to PTV (alt days)	Late toxicity 12–15 months	Recruiting
CYBERPROST, Milecki (PL) [32]	2013	Single centre	600	CK Fiducials	NS	bPFS 5 years	Recruiting
PR-PROS, Collins (US) [33]	2012	Single centre Observational	200	CK Fiducials	35–36.25 Gy/5#	QOL 2 years	Active
Rashtian (US) [34]	2013	Single centre	167	CK Fiducials	36.25 Gy/5 # to PTV	Toxicity bPFS 5 years	Recruiting
Woodhouse (US) [35]	2008	Single centre Phase II	100	CK Fiducials	36.25 Gy/5 #	Toxicity/bPFS 5 and 10 years	Unknown
Chua (SG) [36]	2013	Single centre Phase II	80	Linac	36.25 Gy/5 # over 10–11 days	Late toxicity 2 years	Recruiting
Heron (US) [37]	2010	Single centre Phase II	111	CK Fiducials	36.25 Gy/5 # over 2 weeks	Toxicity/bDFS 2 years	Recruiting
Potters (US) [38]	2010	Single centre Phase I	36		Dose level 1: 40 Gy/5 # (alt days) Dose level 2: 45 Gy/5 # Dose level 3: 50 Gy/5 #	Maximum tolerated dose	Active Results [39, 40]

RAD1203, Fiveash (US) [41]	2013	Single centre Pilot	25	Linac	36.25 Gy/5 # over 1–2 weeks SIB to area containing tumour 40 Gy/5 #	Acute toxicity	Active
Orecchia/Jereczek (IT) [42, 43]	2014	Single centre	65	CK/Linac	36.25 Gy in 5 # over 10 days SIB to dominant lesions 37.5 Gy in 5 #	Acute toxicity	Active
Zelefsky (US) [44]	2017	Single centre Phase I	30	Linac	40 Gy in 5 # SIB to MRI defined lesions 45 Gy in 5 #	Toxicity	Recruiting
Ritter (US) [45]	2015	Single centre Phase I/II	160		40 Gy in 5 # (36.25 Gy urethral sparing) SIB to MRI defined lesions 8.5–9 GY per # 37.5 Gy uniform dose (patients not having MRI)	Toxicity bPFS at 5 years	Recruiting Results [46]
Fuller (US) [47]	2007	Multicentre Phase II	253 (259)	CK Fiducials	38 Gy/4 # Virtual HDR technique (DMax 57 Gy)	bDFS/toxicity 10 years	Active Results [48, 49]
Fuller (US) [50]	2006	Single centre Phase II	258	CK Fiducials	38 Gy in 4 # Virtual HDR technique	Toxicity/QOL bDFS at 5 years	Recruiting Results [51]
2STAR, Loblaw (CA) [52, 53]	2014	Single centre Phase I/II	30	Linac Fiducials/CBCT/ endorectal immobilisation device	26 Gy/2 # weekly	QOL 5 years	Active
eHYPO, Sanguineti (IT) [54]	2015	Single centre Phase I/II	59	Linac Fiducials/CBCT/urethral catheter/rectal gel spacer	40 Gy/3 # (alt days)	GU toxicity 1 year	Recruiting
ONE-SHOT, Zilli (CH) [55]	Due 2017	Single centre Phase I/II	45	Linac Calypso	19 Gy in one # 17 Gy to urethra PRV	Acute toxicity bPFS 3 years	Not yet recruiting
Mantz (US) [56]	2006	Multicentre Phase II	350	SBRT NS	Low risk: SBRT 40 Gy in 5 # Int-risk: IMRT 45 Gy in 25 # and SBRT 22 Gy in 4 #	Toxicity up to 10 years	Recruiting
CKNO-PRO, Lartigau (FR) [57]	2010	Multicentre Phase II	76	CK/Linac	SBRT boost 18 Gy in 3 # over 5–9 days following conventional EBRT 46 Gy in 23 #	Toxicity 2 years	Active Results [58]

CK CyberKnife, *NS* not specified, *HDR* high-dose rate, *PRV* planning organ at risk volume, *GU* genitourinary

Table 14.3 Non-randomised trials involving high risk prostate cancer patients

Trial/PI	Year open	Study design	Target accrual	Risk group	Technique	ADT/Duration	Schedule	Primary objective	Status
Stephans (US) [59]	2012	Single centre	35	L/I/H	NS	Yes As CI	50 Gy in 5 # to high dose PTV 36.25 Gy in 5 # to low dose PTV	Toxicity 1 year	Active Results [60, 61]
Meier (US) [62]	2014	Single centre	146	L/I/H	CK	NS	5 # over 1 week, dose NS	QOL/toxicity 8 years.	Recruiting
Prorate, Nickers (LU) [63]	2014	Single centre Phase II	60	Elderly L/I/H	CK	NS	36.25 Gy/5 # over 10 days, low/intermediate risk 37.5 Gy/5 # high risk	Toxicity 3 years	Recruiting
FASTR-2 Bauman (CA) [64]	2014	Single centre Phase II	60	H	Linac CBCT	18 months	35 Gy in 5 # prostate over 5 weeks	Toxicity 1 year	Recruiting
pHART8, Loblaw/Jain(CA/UK) [65]	2011	Multicentre Phase II	30	H	Linac	NS	40 Gy/5 # prostate weekly 30 Gy in 5 # SV	Acute rectal toxicity	Active
Ong (CA) [66]	2013	Single centre Phase I	77	H	NS	NS	36.25 Gy in 5 # to PTV SIB to MRI defined lesions 40 Gy in 5 #	QOL (EPIC)	Not yet recruiting
SPARC, Van As (UK) [67]	2013	Single centre Phase II	20	I/H	CK	Yes	36.25 Gy/5 # to PTV SIB 47.5 Gy/5 # SIB to MRI defined nodules	Acute GU toxicity	Recruiting
Herrara (CH) [68]	2014	Single centre Phase I/II Dose escalation	27	L/I/H	Rectal spacer	NS	36.25 Gy/5 # Phase I: SIB 45 Gy/5 # escalating to 50 Gy/5 # Phase II: SIB MTD from phase I	Phase I: MTD Phase II: Acute toxicity	Recruiting
King (US) [69]	2014	Multicentre Phase II	220	H	NS	≥9 months	40 Gy in 5 # over 2 weeks 25 Gy to pelvic nodes (as indicated)	bPFS 3 and 5 years Toxicity/QOL 5 years	Recruiting Results [70, 71]
FASTR, Bauman/Rodrigues (CA) [72]	2011	Single centre Phase II	19	H	Linac CBCT	12 months	40 Gy/5 # weekly to prostate 25 Gy in 5 # pelvis (PTV = CTV + 5 mm)	Toxicity 3 years	Terminated results [73]
SATURN Loblaw (CA) [74]	2013	Single centre Phase II	30	H	Linac	12–18 months	40 Gy/5 # prostate 25 Gy /5 # pelvis over 4 weeks	Acute toxicity 3 months	Active Results [75]

Hanna (US) [76]	2015	Single centre Phase I Dose escalation	50	H	Linac CBCT	24 months	47.5 Gy in 5 # prostate. Dose level 1: 22.5 Gy pelvis/50 Gy SIB. Dose level 2: 27.5 Gy pelvis/55 Gy SIB	Maximum tolerated dose	Recruiting
AASUR McBride (US) [77]	2016	Multicentre Phase II	58	H	NS	Yes	SBRT with 6 months Leuprolode, Abiraterone and ARN-509 (Apalutamide)	Biochemical failure 3 years.	Recruiting
Hirsch (US) [78]	2014	Single centre	72	I/H	CK boost	Yes As CI	Int risk: 36.35 Gy/5 # prostate monotherapy. High risk: EBRT 45–50.4 Gy/25–28 # prostate +/−pelvis and 21 Gy/3 # SBRT prostate boost	bDFS at 5 years.	Recruiting
Harsolia (US) [79]	2012	Single centre	167	L/I/H	CK boost	Yes	Low/int risk: 36.25 Gy/5 # prostate monotherapy. High risk: EBRT 50.4 Gy/28 # and 25.5 Gy/5 # SBRT prostate boost	Toxicity/ bPFS 5 years	Recruiting
Eade (AU) [80]	2014	Single centre Phase I Dose escalation	60	NS	Linac Calypso	NS	SBRT prostate boost then 46 Gy in 23 # prostate/pelvis. Dose level 1: 20 Gy/2 # PTV and 22 Gy GTV. Dose level 2: 22 Gy PTV, 27.5 Gy GTV. Dose level 3: 24 Gy PTV, 30 Gy to GTV	Acute toxicity	Recruiting

CI clinically indictaed, *PTV* planning target volume, *CTV* clinical target volume

published this year at 27.6 months median follow up, demonstrated grade 3 late GI toxicity in one patient, and no grade 3 acute or late GU toxicity [25]. The Florida Robotic Radiosurgery Association are conducting a prospective observational trial involved a multi-institutional registry for prostate cancer SBRT, expecting to recruit 3000 patients [28]. The primary aim of this large study is to determine overall survival at 5 years follow up.

The number of current trials delivering SBRT using CyberKnife or linear accelerator are relatively equal. Linac-based techniques offer advantages in terms of treatment time and patient accessibility, however, it is unclear whether the choice of platform contributes to beneficial treatment outcomes. Lukka et al. were due to open a randomised trial in 2015 to compare SBRT in low/intermediate prostate cancer delivered with CyberKnife or with volumetric modulated arc therapy (VMAT) [9]. The primary objective is to assess patient acceptability of the trial, aiming to recruit 40 patients, although according to the clinicaltrials.gov listing, the recruitment status is currently unknown.

There are a variety of image guidance techniques employed within the trials (Table 14.1). Some of the linac-based trials include intra-fraction tracking of prostate motion using Calypso electromagnetic beacons [24, 26, 55]. Lagerwaard et al. are using stereotactic MR-guided adaptive radiation therapy (SMART) within a phase II trial, involving daily plan re-optimisation. In an interim analysis of 16 patients, they demonstrated that plan reoptimisation improved sparing of the rectum and bladder from high doses in around 20% of fractions [81]. A few trials have included the use of injectable rectal spacers or endorectal immobilisation devices in an attempt to reduce prostatic motion and improve rectal dosimetry. Kang et al. are comparing these techniques in a randomised trial, aiming to evaluate differences in toxicity rates [14].

14.2 Comparing SBRT with Standard Treatment

Ultimately, large randomised trials are required to directly compare prostate SBRT outcomes with conventional treatment modalities and fractionation. The Prostate Advances in Comparative Evidence (PACE) trial is an international, multicentre, phase III trial, sponsored by the Royal Marsden Hospital, consisting of two randomisation groups [1]. Within PACE A, low- and intermediate-risk patients are randomised between surgery with radical prostatectomy, and SBRT; or in PACE B randomised between SBRT and conventionally fractionated radiotherapy (Fig. 14.1). All patients are treated without androgen deprivation therapy (ADT). In keeping with the majority of published trials, SBRT patients are treated with 36.25 Gy in five fractions prescribed to the PTV, ensuring 40 Gy to the CTV, delivered with either CyberKnife or Linac based techniques. In the conventional radiotherapy arm, patients are treated with 78 Gy in 39 fractions or 62 Gy in 20 fractions, following publication of the CHHIP trial data in 2016 demonstrating moderate hypofractionation to be non-inferior to conventional fractionation [82]. Patients will be followed up over 10 years and be assessed with PSA, clinician reported measures of acute and late toxicity (CTCAE, RTOG) and patient reported quality of life scores (IIEF, Vaisey, IPSS, EPIC).

Given the difficulties of a surgery versus radiotherapy randomisation, PACE A recruitment has been lower than anticipated. As a result, the primary endpoint of this group has been changed from biochemical disease-free survival (bDFS) to a quality of life endpoint, in order to reduce the recruitment target to 234. In contrast PACE B has recruited exceptionally well, having opened in 40 centres in UK, Ireland and Canada. It has now closed to accrual, having reached the recruitment target of 858 patients by the end of 2017.

Four other randomised trials have been identified, comparing five fraction SBRT with conventionally fractionated or moderately hypofractionated EBRT. A small Hong Kong based phase II trial led by Poon, et al., is currently recruiting low- and intermediate-risk patients within the Asian population [6]. Randomisation is between IMRT 78 Gy in 38 fractions and SBRT 36.25 Gy in five fractions, with a primary outcome measure of health-related quality of lie (QOL) at 1 year. HEAT [4] is a multicentre
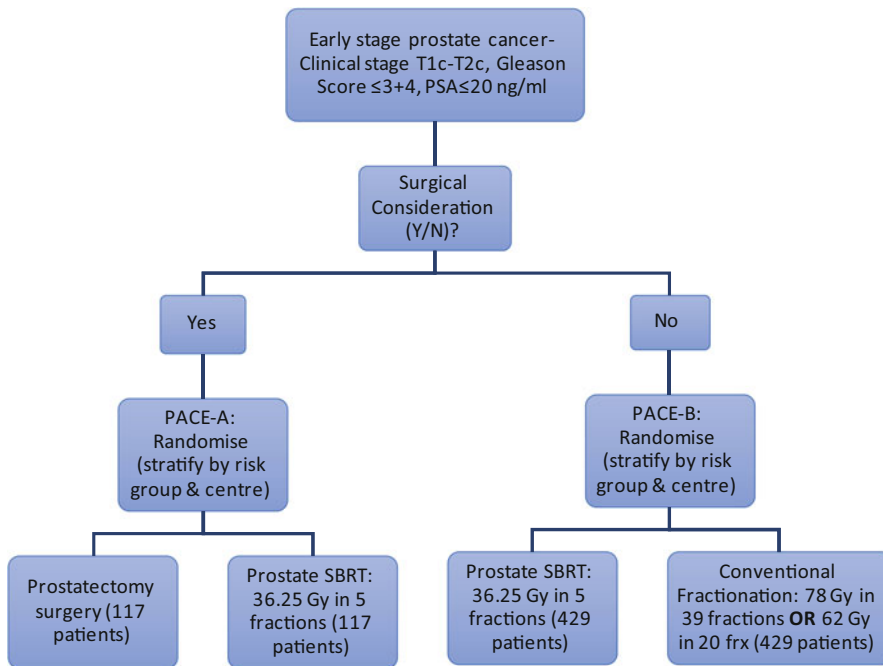
Fig. 14.1 PACE trial schema (taken from the PACE trial protocol, version 9.0, June 2017)

randomised trial from the US which opened in 2013, hoping to recruit 456 patients to determine whether SBRT 36.25 Gy in five fractions is non-inferior to 70.2 Gy in 26 fractions in terms of biochemical or clinical failure rate at 2 years. A further US trial led by Ellis et al. which has yet to recruit will compare SBRT in five fractions and IMRT in 28 fractions with the aim of demonstrating superiority of SBRT in terms of GU/GI toxicity [5]. Early results from The RTOG 0938 trial by Lukka et al., have been published in abstract form in 2016 [2, 3]. 255 patients with low risk prostate cancer were randomised between SBRT, 36.25 Gy in five fractions or a hypofractionated dose of 51.6 Gy in 12 fractions. Both fractionations were well tolerated in terms acute and late toxicity, and patient-reported bowel and urinary outcomes at 1 year.

Although not strictly SBRT, HYPO is Scandinavian-based phase II randomised multicentre trial, comparing a highly hypofractionated schedule of 42.7 Gy in seven fractions on alternate days, with conventional fractionation (78 Gy in 39 fractions) [7]. Recruitment is now

closed having accrued 1200 patients with intermediate-risk prostate cancer (stage T3a disease also permitted). Treatment delivery was with either 3D conformal radiotherapy or VMAT, without the use of concomitant ADT. Two-year acute and late toxicity data has been published with a median patient follow up of 4.2 years [83]. No significant difference in toxicity was found between the two arms at 2 years follow up, which included 866 patients. RTOG $\geq$ grade 2 urinary toxicity was 5.4 and 4.6% for the hypofractionated and conventional arms respectively, and bowel toxicity 2.2 versus 3.7%. In results presented at ESTRO (2018) ultra hypofractioanted schedule was shown to be non-inferior to conventional fractionation at 5 years, in terms of freedom from biochemical or clinical failure, with no significant difference in toxicity rate at 4 and 6 years.

LDR brachytherapy is a standard treatment option for suitable patients with low- and intermediate-risk prostate cancer. This is being compared to SBRT within a small randomised trial based in Finland (BRAVEROBO), now

closed to recruitment [8]. Patients are randomised between LDR brachytherapy using I125 seeds, and SBRT 36.25 Gy in five fractions. The primary aim of this study is to detect any differences in acute and late toxicity between the two groups.

14.3 High-Risk Patients

Currently, there is limited data regarding the use of SBRT in high-risk prostate cancer, defined within the National Cancer Care Guidelines (NCCN) as patients with at least one high-risk feature: Gleason 8–10; clinical stage $\geq$T3a; or PSA >20 ng/ml [84]. Concerns about achieving adequate coverage or potential increased toxicity may have deterred the development of SBRT in this group given the higher risk of disease outside the prostate. Only a few published SBRT studies involve a mixed population which include a small percentage of high risk patients. The pooled multi-institutional analysis of 1100 patients by King et al. was encouraging, demonstrating 81% 5 year bPFS in the high-risk group which made up 11% of the population [85].

Four randomised trials have been identified, which include the delivery of prostate SBRT as monotherapy in high risk patients, all using a dose of 36.25 Gy in five fractions to the PTV (see Table 14.1). The ASSERT trial, which is a Canadian multi-centre trial, aims to compare toxicity from SBRT with a more conventionally fractionated schedule of 73.68 Gy in 28 fractions, in intermediate- and high-risk patients [15]. Table 14.3 summarises ongoing non-randomised trials involving high-risk patients. Of the 20 trials listed, eight have been identified delivering SBRT in five fractions to the prostate alone, where specified at a dose of 35–50 Gy. In some studies, this includes the delivery of a simultaneous integrated boost (SIB) to intraprostatic lesions. Four studies include a mixed group of low-, intermediate- and high-risk patients [59, 62, 63]. Nickers et al., are aiming to determine toxicity in the elderly population. In this trial, low- and intermediate-risk patients are treated at a dose of 36.25 Gy in five fractions which is increased to 37.5 Gy for high risk patients [63].

The largest trial specifically evaluating efficacy and safety of SBRT in the high-risk group, is a multicentre trial phase II trial led by King et al. [69]. They expect to recruit 220 patients, delivering SBRT to the prostate at a dose of 40 Gy in five fractions over 2 weeks. Concomitant androgen deprivation therapy (ADT) and SBRT to the pelvis using a dose of 25 Gy in five fractions, are given at the discretion of the treating clinician. Preliminary results have been published in abstract form in 2017 [70, 71]. Seventy three patients had been treated with a median follow up of 13.8 months. 32% received nodal irradiation and 63% received androgen deprivation therapy (ADT). Overall treatment was well tolerated with no grade 3 GU or GI toxicity seen. 2.7% had evidence of biochemical failure however longer follow up is required to evaluate the efficacy of treatment. The use of ADT or nodal irradiation did not appear to have a significant effect on toxicity, although numbers are too small to draw any conclusions about this. Trials investigating the use of ADT and pelvic SBRT will be discussed later in the chapter.

14.4 Dose Escalation

Dose escalation has been shown to improve biochemical disease-free survival and delay the need for systemic therapy following conventionally fractionated radiotherapy [86–88]. Pollack et al. demonstrated higher rates of freedom from biochemical failure and distant metastases in intermediate- and high-risk patients receiving 78 Gy compared to 70 Gy in 2 Gy fractions [87, 89]. Retrospectively collected data by Zelefsky et al., suggest that doses as high as 86.4 Gy are associated with improved outcomes in high-risk patients, even in combination with hormones [88]. However, any benefit from dose escalation does is likely to come with the disadvantage of increased toxicity [86, 87].

Potters et al., have completed accrual to a phase I study evaluating the tolerability of SBRT dose escalation in low- and intermediate-risk prostate cancer [38]. The study has been designed to recruit 7–15 patients to each of three dose levels: 40 Gy in five fractions, 45 Gy in five

fractions, and 50 Gy in five fractions, escalating to the next dose level if no dose limiting toxicity (DLT) after 90 days in the first seven patients enrolled to a specific dose level. Acute toxicity results from the first two dose levels have been published in abstract form [39, 40]. Twelve patients received 40 Gy in five fractions and ten patients 45 Gy in five fractions. Acute grade 2 (CTCAE v3) GU toxicity was seen in 42 and 50% of patients in each dose level respectively, with no grade 3 toxicity and no ≥ grade 2 GI toxicity. Based on these results the dose was escalated to 50 Gy, the results of which are awaited.

There is not a clear argument for escalating to this dose level, particularly in low risk patients. Studies suggest prostate cancer to have an α/β ratio of <2, lower than that of the surrounding normal tissues and hence sensitive to hypofractionation [90–92]. Even assuming an α/β of 2, an SBRT dose of 36.25 Gy in five fractions has a biologically effective dose (BED) of 168, which is higher than 78 Gy in 39 fractions (BED 156), but has a slightly lower BED (124 vs. 130) in terms of late rectal toxicity, assuming an α/β of 3. Escalating the SBRT dose to 50 Gy in five fractions markedly increases the tumour BED to 305 but at the cost of increasing normal tissue BED to 216, hence increasing the risk of significant rectal toxicity. Dose escalation to 50 Gy has previously been evaluated by the Timmerman group who demonstrated significant toxicity in patients receiving higher dose [93, 94]. Over 6% of patients developed high-grade GI toxicity (≥ grade 3), including five patients who required a colostomy.

Heterogeneous planning techniques could enable dose to be escalated in areas not adjacent to sensitive structures. The PACE trial aims to cover at least 95% PTV with the 36.25 Gy prescription dose while delivering 40 Gy to at least 95% CTV [1]. The technique used by Stephans et al., involves the creation of a high dose PTV (HDPTV) which includes PTV > 3 mm from either urethra, bladder or rectum, and a low dose PTV (LDPTV) which includes PTV within 3 mm of these structures. 36.25 Gy in five fractions is prescribed to the LDPTV, and 50 Gy in five

fractions to the HDPTV [59–61]. At 15 months follow up, treatment was well tolerated with low rates of acute and late toxicity in a cohort of 54 patients, of which 30 were high-risk [61]. One patient suffered grade 4 GU and GI toxicity due to prostatic infection, but did have particular risk factors of uncontrolled diabetes and very large prostate (>200 cc). Biochemical failure was seen in four patients (7.4%), all of which were in high-risk group.

Limiting dose escalation to the area of probable disease within the prostate could minimise toxicity and potentially improve efficacy, particularly since there is evidence from retrospective studies that local recurrence following radiotherapy occurs at the site of the primary tumour [95, 96]. In a study of 124 patients with MR imaging pre- and post-radiotherapy, Arrayeh et al. demonstrated the site of the dominant recurrent tumour to be in the same location as the original dominant tumour in eight of the nine patients with disease recurrence [96]. Recently reported results from the FLAME phase III demonstrate no significant increase in toxicity up to 2 years from combining an integrated boost up to 95 Gy to MRI-defined tumour with fractionated radiotherapy 77 Gy in 35 fractions to the entire prostate [97]. Aluwini et al., have previously reported their experience of using SBRT to apply a focal boost to MRI visible tumour [98]. Fifty patients were treated using CyberKnife at a dose of 38 Gy in four fractions, delivering an integrated boost to 14 patients with a dominant tumour nodule visible on MRI, to a mean dose of 47.8 Gy. 6% grade 3 late GU and no grade 3 GI toxicity overall, was reported at 23 months median follow up. Although the number of patients receiving the tumour boost was very small, no increase in toxicity was reported in this group.

Ongoing trials are evaluating the delivery of a simultaneous integrated boost (SIB) in five fractions. Fiveash et al. (RAD 1203) [41] have recruited 25 low/intermediate risk patients to a pilot trial primarily evaluating early toxicity from SBRT with integrated boost to the area in the prostate most likely to be harbouring disease. 36.25 Gy is prescribed to the whole prostate with

an integrated boost of 40 Gy in five fractions. Six trials have been identified which aim to deliver a SIB to dominant lesions within the prostate, as defined by magnetic resonance imaging (MRI) [42, 44, 45, 66–68]. Four of these are currently recruiting. In the intermediate risk setting, Zelefsky et al. are conducting a phase I feasibility study, treating the whole prostate with 40 Gy in five fractions and applying a SIB of 45 Gy [44]. The SPARC trial which includes intermediate and high risk patients, aims to boost dominant tumour nodules up to 47.5 Gy in five fractions, while delivering 36.25 Gy to the prostate and proximal SV [67]. The primary outcome measure is acute GU toxicity up to 12 weeks post SBRT. In the phase I part of a study led by Herrara et al. in Switzerland, 36.25 Gy is given to the prostate, and the SIB dose is escalated from 45 Gy up to 50 Gy in five fractions, to determine the maximum tolerated dose [66]. Within phase II, patients are treated at the highest tolerated dose in order to determine rate of $\geq$ grade 2 acute toxicity (CTCAE v 4.0).

Ritter et al. use IMRT to combine urethral-sparing, and SIB techniques in a non-randomised phase I/II study, expecting to recruit 160 intermediate/low risk patients [45]. Patients that undergo a pre-treatment MRI are treated with 40 Gy in five fractions on alternate days to the prostate, with the dose to urethra, anterior rectal wall and bladder base limited to 36.25 Gy. A SIB of 42.5 Gy–45 Gy is delivered to MRI defined prostatic lesions. Patients unable to have a MRI are treated with a uniform dose of 36.25 Gy in five fractions. In an analysis of the first 16 patients, the SIB approach was found to be feasible in the ten patients able to undergo MRI [46]. At 8 months median follow up, there was no reported grade 3 or 4 toxicity, and only two patients with grade 2 acute urinary symptoms, although it is not reported which technique these patients were treated with.

14.5 Overall Treatment Time and Fractionation

The effect of overall treatment time in prostate SBRT is not yet known. Published and ongoing trials differ, with many using at least alternate day fractionation schedules. There is however no clear evidence that treating on consecutive days is detrimental, and either consecutive or alternate day fractionation is permitted with the PACE trial. Two multicentre randomised trials are evaluating the influence of weekly fractionation in comparison to alternate day fractionation. The Canadian-based PATRIOT trial has recruited 152 low- and intermediate-risk patients to receive prostate SBRT 40 Gy in five fractions, randomising between treatment over 11 or 29 days [10]. Toxicity (RTOG) and QOL (EPIC) results have been reported at median follow up of 13.1 months [11]. The 29-day arm was found to be superior in terms of patient-reported acute bowel and urinary toxicity, although no significant difference in late toxicity was found between the two schedules. A similar European trial by Mirabell et al. has also completed recruitment, randomising patients from all risk groups to receive 36.25 Gy in five fractions in either 9 days or 28 days [16].

Since prostate cancer is thought to have a low alpha/beta ratio, and therefore particularly sensitive to larger fraction size, the logical next step is to investigate the use of more extreme hypofractionation.

SBRT delivery using a dose of 38 Gy in four fractions has previously been reported [98, 99]. In two large trials led by Fuller et al., SBRT with CyberKnife is delivered at a dose of 38 Gy in four fractions, using a heterogeneous planning technique to emulate HDR brachytherapy [47, 50]. Five year outcomes from the multicentre trial have recently been published in abstract form, having completed accrual of 259 patients [48]. 100% bPFS was demonstrated in low risk patients and 88.5% in intermediate risk. 3% grade 3 GU toxicity and one case of grade 4 GU toxicity were demonstrated and although obstructive GU and GI QOL was similar to baseline, 10% urinary incontinence was detected compared to 2% at baseline. The second study continues to recruit, aiming for an accrual of 258 patients. Five year outcomes have been reported after treating 79 patients, demonstrating bPFS of 98% and 92% in low and intermediate risk patients respectively. Toxicity was acceptable although 6% late grade 3 GU toxicity was reported [51].

High-dose-rate brachytherapy (HDR-BT) delivered in either three fractions of 10.5 Gy or two fractions of 13 Gy, has been shown by Hoskin et al. to have acceptable rates of biochemical control and toxicity at 3 years post treatment [100]. Within the SBRT setting, recruitment is ongoing to an Italian-based phase I/II trial (eHYPO) investigating the tolerability and efficacy of three fraction SBRT, at a total dose of 40 Gy delivered on alternate days [54]. SBRT delivery is with VMAT using cone-beam CT (CBCT) with fiducial markers for image guidance, and includes insertion of rectal gel spacer and urinary catheter to aid accurate urethra delineation. In the 2STAR trial led by Loblaw et al., 26 Gy in 2 weekly fractions is given, aiming to determine QOL at 5 years [52].

At the most extreme, Hoskin et al. have also demonstrated acceptable levels of toxicity after single dose HDR-BT, although did note higher rates of urinary toxicity compared to a two fraction schedule, and in those patients treated with 20 Gy compared to a 19 Gy single-fraction [101]. Single fraction SBRT is currently being assessed in a phase II randomised control trial (PROSINT) led by Greco et al. in Portugal [12]. Using a urethral-sparing planning technique, intermediate-risk patients are randomised to receive SBRT with either 45 Gy in five fractions, or a 24 Gy single fraction. SBRT delivery is with VMAT, using rectal balloon immobilisation and urethral catheter loaded with beacon transponders for tracking. The accrual target is 30 patients, primarily to determine toxicity up to 5 years post treatment. In addition, a diffusion-weighted MRI is performed 15 min after the first treatment to determine early physiologic changes, and biopsy performed 2 years post treatment to evaluate pathologic response. A further single–arm trial (ONE-SHOT) by Zilli et al., was due to open in 2017 [55]. Using similar image guidance and planning techniques, they aim to deliver 19 Gy in one fraction to the prostate and proximal SV, and 17 Gy to the urethral planning risk volume (PRV).

14.6 Combining SBRT Boost with Conventional Radiotherapy

There is randomised trial evidence that an HDR-brachytherapy boost combined with EBRT can improve relapse-free survival compared with EBRT alone in intermediate- and high-risk prostate cancer [102]. Based on this data a number of trials are evaluating dose escalation using SBRT as a boost to the prostate in addition to conventionally fractionated EBRT. There is substantial variation in study design and SBRT dose used within these trials. In three trials treatment is allocated based on risk group. In a multicentre trial by Mantz et al. aiming for 350 patients, treatment low risk patients are treated with SBRT monotherapy, 40 Gy in five fractions, and intermediate risk patients with IMRT 45 Gy in 25 fractions over 5 weeks, followed by an SBRT boost of 22 Gy in four fractions [56]. Harsolia et al., aim to deliver 36.25 Gy in five fractions SBRT monotherapy to low/intermediate-risk patients, and 50.4 Gy in 28 fractions followed by an SBRT boost of 27.5 Gy in five fractions to high risk patients, with hormone therapy as indicated [79]. Hirsch et al., are using a three fraction SBRT boost of 21 Gy delivered following pelvic irradiation in high risk patients, combined with ADT [78]. In the BOOSTER trial the SBRT boost is given prior to EBRT and is escalated from an initial dose level of 20 Gy in two fractions to the PTV and 25 Gy to the GTV if identified [80]. Once acceptable toxicity has been established, the dose is escalated to a maximum of 24 Gy in two fractions to the PTV and 30 Gy to the GTV, with a primary outcome measure of ≥grade 3 RTOG acute toxicity rate.

Two randomised trials based in Poland aim to determine efficacy from delivery of a prostate boost using SBRT in comparison to standard fractionation. HYPOPROST is a large, multicentre trial aiming to randomise 465 patients to receive either a hypofractionated boost of 15 Gy in two fractions, or a conventionally fractionated boost of 30 Gy in 15 fractions, following IMRT to the

whole pelvis using 46 Gy in 23 fractions in combination with ADT [19]. A further trial by Suwinski et al., which has not yet opened to recruitment, is due to compare conventional EBRT alone at 76–78 Gy in 38–39 fractions, with conventional EBRT 76–78 Gy in 38–39 fractions in addition to a boost of 20 Gy in two fractions given with brachytherapy or SBRT [18].

Within the BLaStM randomised trial, Pollack et al. are treating patients either with EBRT 76 Gy in 38 fractions and a SIB of 91.2 Gy in 38 fractions to the MRI defined GTV, or EBRT 76 Gy in 38 fractions preceded by a single stereotactic boost of 12–14 Gy to MRI defined GTV [20]. The primary aim of the trial is to compare the rate of pathologic complete response between the two treatment arms.

14.7   Pelvic SBRT

The role of prophylactic pelvic node irradiation remains controversial. Conventionally fractionated pelvic radiotherapy is sometimes considered in those patients at higher risk of harbouring micrometastatic disease within the pelvis, however, there is currently no conclusive evidence with regard to efficacy, and there is an associated increased risk of bowel toxicity. Ongoing trials are investigating the use of pelvic SBRT in high-risk patients. As previously mentioned, the trial for high risk patients by King et al. includes pelvic SBRT 25 Gy in five fractions to the pelvis, as directed by the treating clinician [69–71]. Treatment was well tolerated by the initial 23 patients who received pelvic SBRT, although median follow was short at 13.8 months [71].

In the FASTR trial, 16 high risk patients were treated with linac-based SBRT to the prostate and pelvic nodes, in combination with 12 months ADT [72, 73]. 40 Gy in 5 weekly fractions was delivered to the prostate and SV, and 25 Gy in 5 weekly fractions to the pelvic nodes. Unfortunately, the trial was terminated due to higher than expected toxicity at 6 months. There was no

≥ grade 3 acute toxicity but one patient suffered grade 3 late GU toxicity, and four patients experienced ≥ grade 3 late GI toxicity. As a result, the currently recruiting phase II trial (FASTR2) does not include pelvic SBRT and the prostate dose has been reduced to 35 Gy [64]. Possible factors contributing to the excessive toxicity include a large CTV-PTV margin of 5 mm, the use of CBCT without fiducial markers, and the inclusion of relatively frail patients within the study. Loblaw et al. have employed the same dose fractionation within the SATURN trial, delivering 40 Gy to the prostate/SV and 25 Gy to the pelvis in 5 weekly fractions, with 12–18 months of ADT [74]. In this trial, a 3 mm PTV margin has been applied to the prostate and 6 mm to the lymph nodes. Both CBCT and fiducial markers have been used for image guidance. Early results from 30 patients suggest that this schedule was reasonably well tolerated, demonstrating no ≥ CTCAE (version 3.0) grade 3 toxicity at 3 or 6 months [75]. At 6 months G2 late GI toxicity was reasonable at 6.9%, although G2 GU toxicity was 34.5% which seems high in comparison with conventionally fractioned or moderately hypofractionated pelvic IMRT as reported by Ferreira et al. [103].

Recently open to recruitment is the SPORT trial, which is a randomised trial evaluating the feasibility of SBRT in high risk prostate cancer, with or without elective nodal irradiation [17]. Thirty high-risk patients are expected to be randomised between SBRT 36.25 Gy in five fractions to the prostate and SV alone, and SBRT 36.25 Gy in five fractions to the prostate/SV in addition to SBRT 25 Gy in five fractions to the pelvic nodes. All patients are treated in combination with ADT. The primary outcomes of the study are to evaluate adequacy of recruitment rate over 2 years, acute toxicity, QOL, and the number of SBRT plans delivered as planned and on schedule. As part of the study blood, urine and prostate tissue will be taken for analysis to investigate potential predictive markers for patients at greater risk of toxicity.

14.8 Combining SBRT with Systemic Therapy

The role of androgen deprivation therapy (ADT) in combination with SBRT for localised prostate cancer is unclear. Evidence for using ADT with standard radiotherapy in low- and intermediate-risk patients is unconvincing, particularly now in the context of dose escalated radiotherapy [104, 105]. In view if this, many of the current prospective SBRT trials in this group, such as the PACE trial, do not include ADT. One exception is the multicentre trial by Tran et al., where 4 months ADT is given in combination with SBRT (36.25 Gy in five fractions) to intermediate-risk patients. Zelefsky et al., have recently commenced recruitment to a multicentre phase III randomised trial to compare SBRT alone or in combination with hormones, in intermediate-risk patients (those with only radiographic evidence of T3 disease are not excluded) [13]. SBRT is given to all patients at a dose of 40 Gy in five fractions, and patients randomised to the SBRT and hormones arm are additionally given 6 months treatment with Degaralix. The primary endpoint of the trial is to determine the number of patients with a positive biopsy at 2 years in intermediate-risk patients.

In high risk prostate cancer, there is greater evidence for the use of ADT in combination with high-dose radiotherapy, as demonstrated by results from the DART trial which supports the use of long-term ADT in these patients [106]. Where specified in currrently ongoing SBRT trials for high-risk patients, ADT is generally administered, either as mandated or at the discretion of the treating clinician (Tables 14.1 and 14.3). There is however variation in the duration of ADT given. In the ASSERT randomised trial, 6 months and 18 months ADT is given alongside SBRT for intermediate- and high-risk patients respectively [15]. In FASTR-2 the duration of leuprolide has been extended to 18 months from 12 months, as used in the initial FASTR protocol, following the reduction in SBRT dose and exclusion of pelvic node treatment as previously discussed [64, 72].

The development of novel androgen-directed therapies given in combination with LHRH analogues, have improved outcomes in castrate resistant metastatic prostate cancer [107, 108]. The next step is to evaluate any potential benefit in the adjuvant setting. The STAMPEDE trial has demonstrated a survival advantage from giving up-front Abiraterone in combination with LHRH analogues in patients presenting with advanced prostate cancer [109]. Notably, this benefit was also seen in those patients receiving radiotherapy for non- metastatic disease. The currently recruiting AASUR trial is combining Abiraterone and Apalutamide (ARN-509), with Leuprolide and SBRT to determine efficacy in very high risk localised prostate cancer [77]. Abiraterone works by inhibiting CYP17 which is an important enzyme involved in androgen production, and Apalutamide is a competitive androgen receptor antagonist. Patients begin the drug combination 3 months before SBRT, continuing for a total of 6 months.

14.9 Conclusion

SBRT research in localised prostate cancer is rapidly evolving. There is substantial evidence demonstrating SBRT to be a safe and effective treatment in low- and intermediate-risk patients, although questions remain regarding optimal technique, dose and fractionation. However, before SBRT can be internationally classified as a standard treatment option, it is vital to confirm at least equivalence with surgery and conventionally fractionated radiotherapy. Results of randomised trials such as the PACE trial are therefore eagerly anticipated.

Evidence for SBRT in high risk patients is much less developed, although the number of ongoing prospective trials in this setting is encouraging. Larger randomised trials are required to compare SBRT with conventional fractionation, and many questions remain with regard to dose, target coverage including the need for pelvic SBRT, and the potential benefit of combining SBRT with systemic therapy.

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