ANTICANCER RESEARCH *38*: 1231-1240 (2018)
doi:10.21873/anticanres.12344

Review

Stereotactic Body Radiation Therapy for Patients with Early-stage Prostate Cancer

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Abstract. *Aim: Stereotactic body radiation therapy (SBRT) is emerging as a new treatment option for early-stage prostate cancer, theoretically providing clinical and economic benefits compared to conventionally fractionated external-beam radiation therapy (CF-EBRT). This review aimed to evaluate available published data to determine if the proposed theoretical benefits translate clinically. Materials and Methods: A systematic search strategy was employed across three databases using predefined search terms, inclusion and exclusion criteria to identify relevant articles. Results: Sixteen articles were included. Biochemical progression-free survival rates of 77.1-100% were reported in SBRT studies compared to 55-98% in CF-EBRT studies. Incidence of acute grade 1, 2, and 3 genitourinary toxicities were reported in the range of 13.3-71%, 12-25% and 0-3%, respectively, in the SBRT cohort in comparison to 28.7-51.9%, 15.6-41.4%. and 1.1-8.1%, respectively, in the CF-EBRT cohort. Incidence of acute grade 1, 2, and 3 gastrointestinal toxicities were reported in the range of 13-67%, 1-27% and 0-9%, respectively, of the SBRT cohort compared to 16.1- 51.1%, 6.3-20.7% and 0-3%, respectively, of the CF-EBRT cohort. Mean treatment costs estimates associated with SBRT ranged from $22,152 to $24,873 and $33,068 to $35,431 for CF-EBRT. Conclusion: Available data support the hypothesis of lower rates of acute toxicity and reduced economic burden associated with SBRT compared to CF-EBRT, however, randomised data with longer follow-up are needed to determine whether SBRT is clinically more effective than CF-EBRT.*

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Key Words: Prostate cancer, stereotactic, SBRT, review.

Prostate cancer is the second most common malignancy in males, with increasing numbers of patients being diagnosed with early-stage disease (1, 2). Current potentially curative therapeutic options for these patients include conventionally fractionated external-beam radiation therapy (CF-EBRT), radical prostatectomy and brachytherapy (3). Stereotactic body radiation therapy (SBRT) is emerging as a new treatment option (4).

Current treatment options are considered comparable in terms of 5-year biochemical progression-free survival (bPFS) (3). CF-EBRT is a popular option, chosen by up to 46% of this patient group (5), however, longer treatment durations can be problematic for some patients (5). CF-EBRT involves delivery of a 1.8-2.0 Gy fraction, five days per week for seven to eight weeks to total doses ranging 78-81 Gy (6). SBRT is delivered in higher doses per fraction, ranging from 3.5 to 15 Gy in up to five fractions, and to total doses ranging from 30 to 50 Gy (6). This may be more convenient for patients and may also reduce the resource burden on departments. In 2009, treatment of prostate cancer cost €81 million in Ireland and €116.7 million in the UK in the first year since diagnosis (1,7). Implementation of SBRT as a treatment option could potentially reduce this, increase patient throughput and reduce possible waiting lists.

SBRT also theoretically improves the therapeutic window for these patients, compared to CF-EBRT (8). In theory, an increased dose per fraction improves the tumour control probability of early-stage prostate tumours without increasing the normal tissue complication probability (NTCP) of the rectum and genitourinary (GU) tract, based on their associated α/β ratios (4), which is a radiobiological parameter that explains a tissue's behaviour with respect to a radiation schedule (6). A low α/β ratio can imply greater sensitivity to higher dose fractions, while higher α/β ratios suggest higher

sensitivity to overall dose (9). Multiple publications suggest that early-stage prostate tumours have a low α/β ratio of 1.5, implying greater tumour control probability with increased dose per fraction (9-11), while that of the rectum is estimated at 4-6 (12) and the α/β ratio of the GU tract is estimated at 3-7 (13). As the total dose of SBRT schemes is significantly less than that of CF-EBRT schemes, the NTCP of the rectum and GU tract could potentially be reduced.

Despite these proposed theoretical benefits, physicians are hesitant to adopt this treatment approach for this patient group. There is a lack of certainty that the linear-quadratic model of cell kill, from which the concept of α/β ratios is derived, may be applied to estimating dose–response with very large doses per fraction (4). This study aimed to address these concerns through analysis and comparison of clinical data of SBRT treatment for early-stage prostate cancer to CF-EBRT data.

Materials and Methods

A systematic search was performed across three electronic databases (Science direct, Cinahl and Pubmed) for studies of patients with early-stage prostate cancer treated with SBRT or CF-EBRT. Prospective and retrospective trials published between January 2007 and November 2016, with 40 or more participants were included. Studies reporting rates of low- to high-grade gastro-intestinal (GI) and GU toxicities using the Common Terminology Criteria for Adverse Events (14) or Radiation Therapy Oncology Group (15) scales were included. No published randomised control trials comparing the two interventions were identified. Ten SBRT studies reporting bPFS rates were included and seven SBRT studies reporting rates of acute low- to high-grade GI and GU toxicities. Four CF-EBRT studies reporting bPFS rates were identified and four CF-EBRT studies reporting crude rates of acute low- to high-grade GI and GU toxicities. Two studies using the Markov design analysis model to compare estimated mean costs of the two treatment options were included. The Downs and Black scale was used to assess quality of the studies collected (16).

Results

The primary database search yielded 696 results; 657 articles did not meet the inclusion criteria and were omitted based on title and abstract review. A secondary manual search of reference lists from primary articles, identified a further five articles for inclusion. Following a full text review, 18 studies fit the inclusion criteria. See Figure 1 for details.

Treatment efficacy. Outcome data from eight SBRT studies of patients with early-stage prostate cancer with a combined patient cohort of n=2007 were included (17-24). This included 1,281 low-risk, 622 intermediate-risk and 104 high-risk patients. Rates of bPFS reported ranged from 77.1% to 100% (17-24), at endpoints ranging 2-7 years post treatment.

Four studies reporting outcome data for early stage prostate cancer treated with CF-EBRT with a combined patient cohort of n=1778 were included in this review (27-30). This cohort consisted of 407 low-risk, 1,111 intermediate-risk and 254 high-risk patients. Reported rates of bPFS ranged from 55% to 98%, at endpoints ranging 5-10 years post treatment.

Treatment toxicity. Rates of grade1 GU toxicity reported in SBRT studies (n=1048) ranged from 13.3 to 71% (17,19-23,25), grade 2 from 12 to 25% and grade 3 from 0 to 4%. No grade 4 or higher acute GU toxicities were reported.

Rates of grade1 GU toxicity reported in CF-EBRT (n=1118) studies ranged from 28.7 to 51.9% (30-32), grade 2 from 15.6 to 41.4% and grade 3 from 1.1 to 8%. Two grade 4 acute GU toxicities were reported, a rate of 0.001% in the overall cohort. One CF-EBRT study (n=1065) neglected to stratify rates of GU toxicity by grade; it reported that 46% of patients treated experienced grade 2 or higher acute GU toxicity (29).

Rates of grade 1 GI toxicity reported in SBRT studies (n=1048) were13-67% (17,19-23,25), grade 2 between 1 and 27%, and grade 3 from 0 to 3%.

Rates of grade1 GI toxicities reported in CF-EBRT studies ranged from 16.1 to 51.1% (30-32), grade 2 from 6.3 to 20.7% and grade 3 from 0 to 9%. One CF-EBRT study neglected to stratify rates of acute GI toxicity by grade (29); it reported that 25% of patients treated EBRT experienced grade 2 or higher GI toxicity.

Two out of the four CF-EBRT studies that stated rates of toxicity (n=965) reported interruption of treatment due to severe toxicity in 11 patients (31,32). No SBRT study reported treatment interruption due to incidence of toxicity. Findings from studies on efficacy and toxicity are summarised in Tables I and II.

Treatment cost effectiveness. Two studies were identified that compared estimated mean costs of SBRT and CF-EBRT for early-stage prostate cancer (33, 34). Results from both studies support the hypothesis that SBRT is associated with a smaller economic burden for patients and departments compared to CF-EBRT. One study estimated the mean cost of SBRT treatment for patients with early-stage prostate cancer to be $22,152 compared to $35,431 for CF-EBRT (33). The other study estimated a mean lifetime cost of $24,873 for patients treated with SBRT compared to $33,068 for CF-EBRT (34). One study estimated that if 50% of patients with early-stage prostate cancer in the USA chose this option, annual societal savings of approximately $250 million could be expected (33). No articles were found within the search that discredited this argument.

Discussion

The outcome data presented suggest at least equivalent efficacy of SBRT to CF-EBRT. However, the ability to directly compare outcomes and therefore definitively

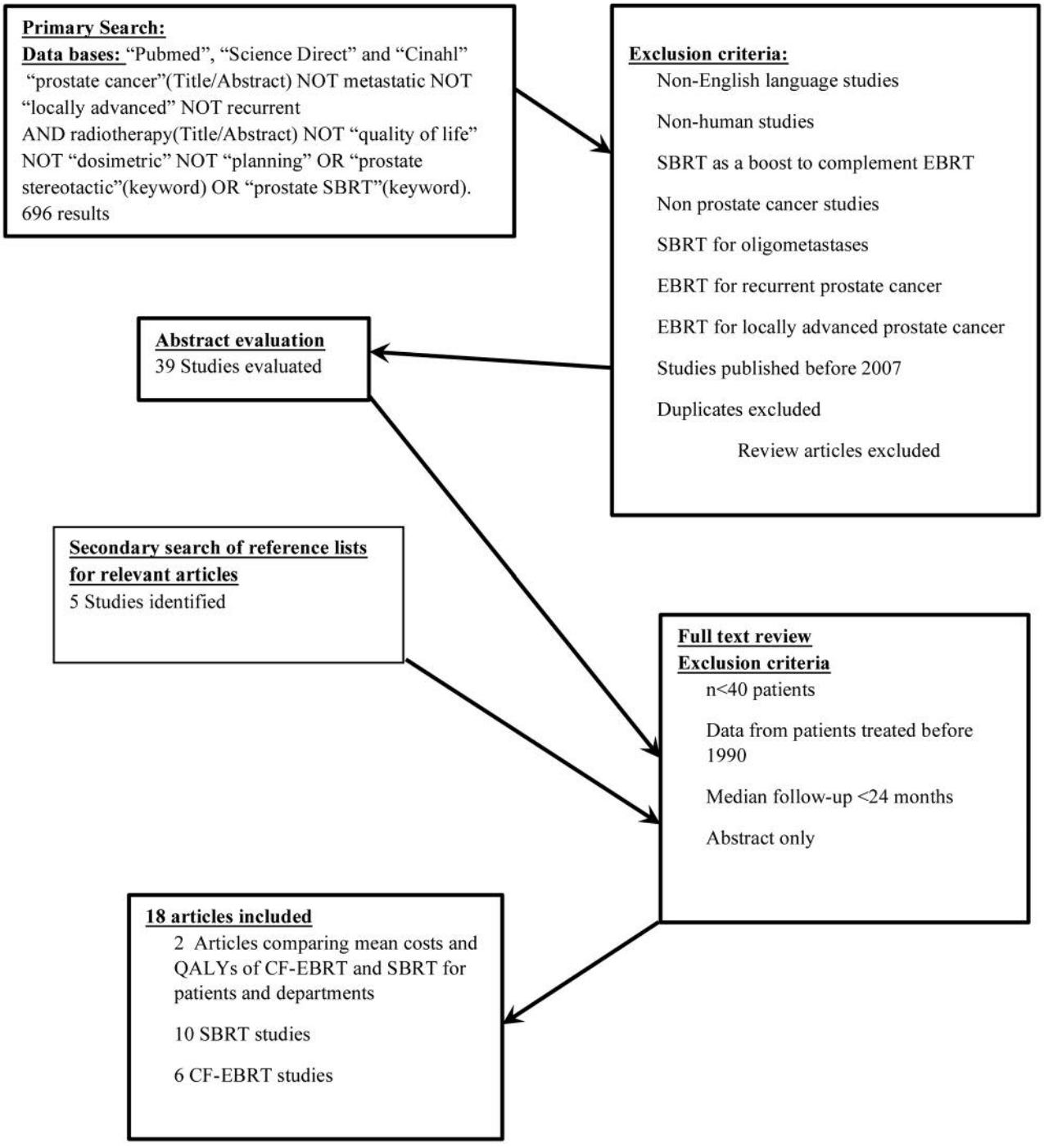

Figure 1. *Database search strategy and results. SBRT: Stereotactic body radiation therapy; EBRT: external beam radiation therapy, QALYs: quality-adjusted life years; CF-EBRT: conventionally fractionated external beam radiation therapy.*

determine if SBRT is more effective is limited. bPFS rates in SBRT studies are reported at varying endpoints, therefore they cannot be directly compared. Five out of the eight SBRT trials (n=1355) reported bPFS at less than 5 years of follow-up (19, 20, 23-25), while it was reported at a minimum of 5 years post treatment in all CF-EBRT studies (27-30).

In studies where rates of bPFS reported were stratified according to risk status, bPFS appears equivalent for both

Table I. *Summary of results from stereotactic body radiation therapy trials included.*

Author (Institution)	Analysis	Patient cohort	Year published	Dose schedule (delivery method)	ADT	Follow-up (median)	bPFS (relapse= nadir+2NG-Phoenix definition)	Acute urinary toxicity	Acute rectal toxicity	Study quality (using Downs Scale-max score 26)
Bolzicco *et al.* (17) (San Bortolo Hospital, Vicenza, Italy)	Phase I/II	n=100 Low risk, n=41 Intermediate risk, n=42 High risk, n=17	2013	35 Gy in 5 fractions daily (CK)	29%	36 Months (range=6-76 months)	(Included in Kings pooled analysis of outcomes)	RTOG: G1, n=34 (34%) G2, n=12 (12%) G3+, 0	RTOG: G1, n=27 (27%) G2, n=18 (18%) G3+ n=0%	14
Loblaw *et al.* (21) (Sunnybrook, Canada)	Phase I/II	n=84 Low risk	2013	35 Gy in 5 fractions Once weekly over 29 days (IMRT)	1%	55 Months (range=13-68 months)	98% @5years (95% CI= 96-100%) One patient experienced biochemical failure	CTCAE: G1, n=60 (71%) G2, n=4 (17%) G3, n=1 (1%)	CTCAE: G1, n=56 (67%) G2, n=8 (10%) G3, 0%	14
Freeman *et al.* (25) (Naples, Florida)	Phase I/II	n=41 Low risk	2011	35 Gy in 5 fractions 36.25 Gy in 5 fractions (CK)	0%	60 months (range=4.2-6.2 years)	(Included in Kings pooled analysis of outcomes)	RTOG: G1, n=10 (25%) G2, n=3 (7%) G3, n=1 (2.5%)	G1, 13% (6/41) G2, 2.5% (1/41) G3, 0%	13
Madsen *et al.* (16) (SHARP trial) (VMMC-Virginia Mason Medical Centre)	Phase I/II	n=40 Low risk	2007	33.5 Gy in 5 daily fractions (3DCRT)	0%	41 months (range=12-60 months)	90% @ 4 years 3 patients experienced biochemical failure (95% CI not documented)	G1, 11 (28%) G2, 8 (20.5%) G3, 1 (2.5%)	G1, 10 (26%) G2, 5 (13%) G3+, 0	14
McBride *et al.* (20) (USA multi-institutional)	Phase I	n=45 Low risk	2012	36.25 Gy in 5 fractions-34 patients (76%) 37.5 Gy in 5 fractions (22%) 1 patient (2%)-dose not stated Completed <10 days (CK)	0%	44.5 months (range=0-62 months)	100% @ 3 years 1 patient died of unrelated causes there were no biochemical failures	CTCAE: G1, 25 (59%) G2, 819%) G3, 0% 42 (93%) patients were available for acute toxicity analysis	CTCAE: G1, 13/42 (31%) G2, 3/42 (27%) G3, 0%	14
King *et al.* (24) Pooled analysis*	Retro-spective	n=1,100 Low risk, n=641 Intermediate risk, n=334 high risk, n=125	2013	35 Gy in 5-n=385 36.25 Gy in 5-n=589 38-40 Gy in 5-n=126 daily (CK)	(14% of all patients) Low-50 (8%), Inter-49 (15%), High- 48 (38%)	Low risk-36 months Intermed -iate risk -30.5 months High risk-23 months	94% @ 3 years 5-year Kaplan–Meier bPFS Low risk, 95.2% Intermediate risk, 84.1% High risk, 81.2%	Not reported	Not reported	17
Chen *et al.* (23) (Georgetown University)	Retro-spective	n=100 Low risk, n=37 Intermediate	2014	35 Gy in 5 fractions (15%) 36.25 Gy in	11%	27.6 months (range=1.4-3.5 years)	99% @ 2 years One biochemical	CTCAE: G 1, 36 (36%) G 2, 35	CTCAE: G 1, 20 (20%) G 2, 1 (1%)	15

Table I. *Continued*

Table I. *Continued*

Author (Institution)	Analysis	Patient cohort	Year published	Dose schedule (delivery method)	ADT	Follow-up (median)	bPFS (relapse= nadir+2NG-Phoenix definition)	Acute urinary toxicity	Acute rectal toxicity	Study quality (using Downs Scale-max score 26)
		Risk, n=55 High risk, n=8		5 fractions (85%) alternate days (CK)			Failure in a high risk patient	(35%) G 3, 0	G 3, 0	
Katz and Kang (18) (Winthrop University Hospital)	Phase I/II	n=477 Low-risk, n=324 Intermediate risk, n=153	2013	35 Gy in 5 fractions n=50 36.25 Gy in 5 fractions n=427 daily (CK)	19%	72 months (range=0-96 months)	93.7% @ 7 years-all patients low risk-95.6% intermediate-risk-89.6% @ 7 years 11 low-risk and 14 intermediate risk experienced biochemical failure	RTOG: G1, not reported G2, not reported G3+, 0	RTOG: G1, not reported G2, not reported G3+, 0	14
Oliai *et al*. (19) (Drexel University College, Philadelphia)	Retro-spective	n=70 Low risk, n=36 Intermediate risk, n=22 High risk, n=12	2013	35 Gy in 5 fractions-n=5 36.25 Gy in 5 fractions-n=36 37 Gy in 5 fractions n=29 daily (CK)	33%	31 months (range=13-51 months)	Low risk-100% Intermediate risk-95% High risk-77.1% @ 3 years 3-biochemical failure	RTOG: G1, 31 (44%) G2, 13 (19%) G3, 3 (4%)	RTOG: G1, 7 (17%) G2, 6 (9%) G3, 2 (3%)	13
Hannan *et al*. (22) (USA-multi-institutional)**	Phase I/II Phase 1, 47 patients Phase 2, additional 47 patients	n=91 Phase 1 45 Gy Low risk, n=3 Intermediate risk, n=12 47.5 Gy Low-n=8 Intermediate risk, n=7 50 Gy Low risk, n=7 Intermediate risk, n=7 Phase 2 Low risk, n=15 Intermediate risk, n=32	2016	45 Gy in 5 fractions 47.5 Gy in 5 fractions 50 Gy in 5 fractions (CK)	16.5%	45 Gy: 74 months 47.5 Gy: 72 months 50 Gy: 66 months	100% @ 3 years 98.6% @ 5 years 1 intermediate-risk patient experienced biochemical failure 40 months after treatment	CTCAE: 45 Gy: G1, 2 (13.3%) G2, 5 (33.3%) G3, 0% 47.5 Gy: G1, 8 (53.3%) G2, 1 (6.7%) G3, 0% 50 Gy: G1, 34 (55.7%) G2, 14 (23%) G3, 0%	CTCAE: 45 Gy: G1, 6 (40%) G2, 1 (6.7%) G3, 0% 47.5 Gy: G1, 4 (26.7%) G2, 4 (26.7%) G3, 0% 50 Gy: G1, 34 (55.7%) G2, 14 (23%) G3, 0%	15

ADT: Androgen-deprivation therapy; bPFS: biochemical progression-free survival; RTOG: Radiation Therapy Oncology Group; IMRT: intensity-modulated radiation therapy; CK: Cyberknife; CTCAE: Common Terminology Criteria for Adverse Events; 3DCRT: 3D conformal radiotherapy; CI: confidence interval. *Participating institutions in the pooled analysis: Flushing Radiation Oncology, Flushing, NY, Naples Radiation Oncology, Naples, FL, Dept. of Radiation Oncology, Beth Israel Deaconness, Boston, MA, Radiosurgery Medical Group, San Diego, CA, Division of Radiation Oncology, San Bortolo Hospital, Vicenza, Italy, Dept. of Radiation Oncology, Stanford, CA, Dept. of Radiation Oncology, Georgetown University, Washington DC, Dept. of Radiation Oncology, Swedish Medical Center, Seattle, WA. **Participating institutions: multi-institutional trial: University of Texas Southwestern Medical Center, University of Minnesota, Prairie Lakes Hospital, University of Colorado, Orlando Health. American Urology Association.

Table II. *Summary of results from conventionally fractionated-external beam radiation therapy trials included.*

Author (Institution)	Analysis	Patient cohort	Year	Dose schedule	ADT	Follow-up (median)	bRFS (relapse= nadir +2NG-Phoenix definition)	Acute urinary toxicity	Acute rectal toxicity	Study quality (using Downs Scale, max score 26)
Leborgne *et al*. (28) (Hospital Italiano in Montevideo, Uruguay)	Retro-spective (reporting data from conventional dose fractionation arm)	n=138 Low-risk, n=59 Intermediate-risk, n=70 High-risk, n=9	2009	median-78 Gy over 55 days (3DCRT) four-field box	40%	49 Months (range, 24-73 months)	Low-risk, 98% (95% CI= 96.9-99.5%) Intermediate-risk, 84% (95% CI= 70.8-98.5%) High-risk, 87% (95% CI= 74-99.9%) @ 5 years	Not reported	Not reported	15
Dearnaley *et al*. (26) (CHHiP trial) international multi-centre	RCT (reporting data from conventional dose fractionation arm)	n=1065 Low-risk, n=157 (15%) Intermediate-risk, n=779 (73%) High-risk, n=129 (12%)	2016	74 Gy in 37 fractions daily (IMRT)	97%	62.6 months (54 months-77 months)	88.3% (95% CI 86.0-90.2) @ 5 Years Low-risk, 96.7% (95% CI=92.3-98.6) Intermediate-risk, 86.8% (95% Cl= 84.0-89.1) High risk-8 6.5% (95% CI-78.4-91.7) 111/1065 had biochemical failure	RTOG: Grade 2+: n=331 (46%)	RTOG: Grade 2+: n=176 (25%)	15
Dearnaley *et al*. (27) (MRC RT01 trial international multi-centre)	RCT (reporting data from conventional dose fractionation arm)	n=422 Low-risk, n=81 (20%) Intermediate-risk, n=152 (36%) High-risk, n=184 (44%)	2014	74 Gy in 37 fractions daily (3DCRT)	100%	10 years	55% (95% CI-50-61)@ 10 years Approximately 80% @ 5years (according to Kaplan–Meier graph, not otherwise documented) 170/421 (43%) experienced biochemical progression	Not reported	Not reported	14
Beckendorf *et al*. (29) (GETUG 06 trial multi-centre France)	RCT (reporting data from conventional dose fractionation arm)	n=153 Intermediate-risk, n=110 High-risk, n=43	2011	80 Gy in 40 fractions (3DCRT) daily	0%	61 Months	76.5% @ 5 years 6 Patients died of prostate cancer by 54 months	RTOG: G1: 32% G2: 24% G3: 3%	RTOG: G1: 34% G2: 21% G3: 9%	16
Jereczek-Fossa et al. (30)	Non-randomised prospective	n=174 Low-risk, n=32	2011	80 Gy in 40 (3DCRT)	69%	Not applicable	Not reported	RTOG: G1: n=72 (41.4%)	RTOG: G1: n=28 (16.1%)	15

Table II. *Continued*

Table II. *Continued*

Author (Institution)	Analysis	Patient cohort	Year	Dose schedule	ADT	Follow-up (median)	bRFS (relapse= nadir +2NG-Phoenix definition)	Acute urinary toxicity	Acute rectal toxicity	Study quality (using Downs Scale, max score 26)
(European Institute of Oncology, Milan, Italy)	Study (reporting data from conventional dose fractionation arm)	Intermediate-risk, n=68 High-risk n=74		daily				G2: n=36 (20.7%) G3: n=1 (0.6%) G4: n=2 (1.1%) (two patients treatment interrupted due to toxicity)	G2: n=11 (6.3%) G3+: 0%	
Matzinger *et al*. (31) EORTC trial 22991 multi-institutional international)	Retrospective	791 Intermediate- and high-risk	2009	70 Gy-78 Gy in 2 Gy/fraction (3DCRT) 74-78 Gy in 2 Gy/ fraction (IMRT) daily	50%	22 months	Not reported	CTCAE: 70 Gy: G1, n=91 (46.7%) G2, n=65 (33.3%) G3, n=14 (7.2%) 74 Gy: G1, n=195 (51.9%) G2, n=131 (34.8%) G3, n=18 (4.8%) 78 Gy: G1, n=37 (45.7%) G2, n=31 (38.3%) G3, n=6 (7.4%) 74 Gy: IMRT G1, n=13 (46.4%) G2, n=7 (25%) G3, n=3 (10.7%) 78 Gy: IMRT G1, 53/111 (47.7%) G2, 46/111 (41.4%) G3, 9/111 (8.1%) (9 patients temporarily interrupted treatment due to acute toxicity)	CTCAE: 70 Gy: G1, n=89 (45.6%) G2, n=45 (23.1%) G3+, 0% 74 Gy: G1, n=192 (51.1%) G2, n=67 (17.8%) G3, n=3 (0.8%) 78 Gy: G1, n=39 (48.1%) G2, n=6 (7.4%) G3, n=2 (2.5%) 74 Gy: IMRT G1, n=11 (39.3%) G2, n=2 (7.1%) G3, 0% 78 Gy: G1, n=42 (37.8%) G2, n=23 (20.7%) G3, n=2 (1.8%)	15

ADT: Androgen-deprivation therapy; bPFS: biochemical progression-free survival; RTOG: Radiation Therapy Oncology Group; IMRT: intensity-modulated radiation therapy; CTCAE: Common Terminology Criteria for Adverse Events; 3DCRT: 3D conformal radiotherapy; CI: confidence interval; RCT: randomised controlled trial.

treatment options among low-risk patients at 5 years of follow-up. However, among intermediate-risk patients, rates appear more favourable in the SBRT cohort than in the CF-EBRT cohort. Further statistical analysis would be required to identify a definitive difference between the treatment options.

At 5 years of follow-up, there was a wider range of bPFS rates reported in CF-EBRT studies. The proportion of low-risk patients included in SBRT trials (64%) was found to be considerably higher than that in CF-EBRT trials (23%). There was also a higher proportion of intermediate-risk (62%) and high-risk (14%) patients included in CF-EBRT trials compared to those treated with SBRT (31% and 5%, respectively). Risk classification stratifies patients according to specific tumour characteristics as a method of predicting outcome (35). It is expected that low-risk patients would experience greater disease control than intermediate- or high-risk patients (35), which may account for more favourable outcomes among the SBRT cohort.

Furthermore, the CF-EBRT studies reported on patients treated between 1990 and 2011 and the SBRT studies between 2002 and 2013.There may be a potential bias in terms of developments in imaging modalities used for staging, grading and treatment delivery during this time.

The quality of evidence supporting SBRT also limits the ability to determine whether it is more effective. Five out of the eight SBRT trials included were single institutional trials (23, 25, 26, 28, 30). Their data is therefore not necessarily generalizable to the entire patient population. Sample sizes within SBRT trials were relatively small; six out of the eight SBRT trials reporting outcomes had 100 or fewer participants (23, 26-30). As sample size is inversely proportional to the margin of error, this is also a limiting factor (36). A single multi-national, multi-institutional pooled analysis of patients treated with SBRT (n=1100) was identified, reporting rates of bPFS at 3 years that are consistent with results reported in other SBRT studies of poorer quality (25).

Toxicity data presented support the hypothesis that lower rates of toxicity are associated with SBRT compared to CF-EBRT, in the acute setting. However, the highest rates of grade1 GI and GU toxicities in an individual study were reported in an SBRT trial (22). This is the only SBRT trial in which treatments were delivered using a standard linear accelerator using online megavoltage portal imaging matched to gold fiducials in the prostate for daily image guidance. In the other SBRT trials included, treatment was delivered using a Cyberknife. Cyberknife allows for precise tumour tracking to sub-millimetre accuracy, compared to millimetre accuracy of other linac-based systems (37). Greater confidence in precise dose delivery to the target volume allows a potential reduction of clinical target volume - planning target volume (CTV-PTV) margins and potentially increased sparing of normal tissue achieved by steeper dose gradients around the PTV (5).

All four CF-EBRT studies included reported use of megavoltage portal imaging for image guidance. Imaging protocols ranged from weekly to once every 2 weeks, compared to daily online imaging in all SBRT trials. It is therefore difficult to determine if lower toxicity rates can be attributed to the theorised radiobiological parameters of the tumours and surrounding tissues or the more robust image guidance and imaging frequency reported in the SBRT trials.

Both studies that analysed cost effectiveness of the treatment options (33,34) used the Markov design analysis model, a very well-recognised method of comparative effectiveness analysis (4). The factors affecting the Markov design analysis model are cost, quality of life and efficacy (bPFS) (4). Both studies assumed SBRT and CF-IMRT were equally effective and associated with equal rates of treatment-induced toxicity, based on the current data available for SBRT. However, given the lack of long-term follow-up, little is known about late effects that could impact negatively on patients' quality of life.

Further studies with longer follow-up are required for formal comparison of SBRT and CF-EBRT in order to definitively determine if SBRT is a more effective and less toxic treatment approach. A limiting factor of this review is that not all participants included received adjuvant androgen deprivation therapy (ADT). In SBRT trials, the number of patients prescribed ADT ranged from 0 to 38% of the given patient cohorts. In comparison, in CF-EBRT studies, 40-100% were prescribed ADT. Level one evidence shows significant improvement of bPFS when patients receive adjuvant ADT compared to RT alone (38). This further demonstrates the need for a randomised controlled trial comparing SBRT with CF-EBRT, within which use of ADT should be protocolled.

Conclusion

Available clinical data of early-stage prostate cancer treatment with SBRT suggest it to be an attractive alternative to CF-EBRT. Longer term follow-up, larger patient cohorts and randomised data are needed to allow direct comparison of the two techniques.

Conflicts of Interest

None.

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Received November 30, 2017
Revised January 8, 2018
Accepted January 11, 2018