Ablative Radiotherapy in Prostate Cancer

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Prostate cancer (PCa) is the most common noncutaneous solid organ malignancy among men worldwide. Radiation therapy is a standard of care treatment option that has historically been delivered in the form of small daily doses of radiation over the span of multiple weeks. PCa appears to have a unique sensitivity to higher doses of radiation per fraction, rendering it susceptible to abbreviated forms of treatment. Stereotactic body radiation therapy (SBRT) and high-dose-rate brachytherapy (HDRBT) are both modern radiation modalities that allow the precise delivery of ablative doses of radiation to the prostate while maximally sparing sensitive surrounding normal structures. In this review, we highlight the evidence regarding the radiobiology, oncological outcomes, toxicity and dose/fractionation schemes of SBRT and HDRBT monotherapy in men with low-and intermediate-risk PCa.

Keywords: prostate cancer, ablative, SBRT, HDR

1. Introduction

Most patients diagnosed with prostate cancer (PCa) in the developed world present with clinically localized disease, and the majority have low- or intermediate-risk disease as defined by the National Comprehensive Cancer Network (NCCN) [1]. External beam radiotherapy (EBRT) is a standard of care option for all patients with localized prostate cancer. Conventionally fractionated EBRT (CF-RT) consists of daily doses or fractions (1.8–2.0 Gy each) delivered over 39–45 treatment sessions. Considerable data suggest that PCa has a low alpha/beta ratio ranging from 1.5 to 3.1 [2], implying a preferential response to higher doses per fraction compared to most other tumors and normal tissues [3]. This has motivated multiple clinical trials investigating higher dose-per-fraction regimens. Moderate hypofractionation (MHF-RT) regimens, which deliver 2.4–3.4 Gy per day over 20–30 treatment sessions, have been studied extensively, with three non-inferiority randomized clinical trials demonstrating the efficacy and safety of this approach [4][5][6] and one superiority trial showing improved outcomes without worse toxicity [7], establishing it as the preferred regimen for localized PCa [8]. Extreme or ultrahypofractionation radiotherapy (UHF-RT) regimens deliver ≥5 Gy per fraction; when advanced delivery techniques and ≤5 fractions are used, the approach is termed stereotactic body radiotherapy or stereotactic ablative radiotherapy (SBRT/SABR). UHF-RT has demonstrated oncologic non-inferiority compared with CF-RT in one randomized trial [9], and SBRT has demonstrated equivalent acute toxicity in another randomized trial [10]. Long-term data from pooled prospective studies [11], as well as a comprehensive meta-analysis [12], suggest a very favorable safety and toxicity profile for SBRT. As of 2020, UHF-RT is now listed as a standard radiation option for all patients with localized disease in the NCCN guidelines [13].

As an alternative to EBRT, prostate brachytherapy involves the placement of sealed radiation sources into the prostate. Radiation intensity follows the inverse square law; therefore, brachytherapy allows very high doses to be delivered intraprostatically, with a sharp dose gradient outside of the prostate establishing high conformity to the target volume. High-dose rate brachytherapy (HDRBT) is a form of brachytherapy in which high-activity radiation sources (e.g., iridium-192) are temporarily placed within the prostate, typically over two to three fractions. Radiobiologically, HDRBT leverages the low alpha/beta ratio of prostate cancer as well. HDRBT as a monotherapeutic option has been investigated in multiple institutional series [14][15]. As of 2020, it is considered a standard option for very low, low, and favorable intermediate risk disease per the NCCN guidelines [13].

2. Radiobiology of Ablative Radiotherapy

There are several advantages of ablative radiotherapy (SBRT or HDRBT) compared to conventionally fractionated radiotherapy when treating prostate cancer. First of all, prostate cancer preferentially responses to higher doses per fraction of radiation compared to most other tumors and normal tissues given its low alpha/beta ratio (typically 1.5 to 3.1) [16]. Secondly, ablative RT is delivered over a much shorter period of time. Although this is not as dominant as a factor compared to fraction size for late-responding tissues, there is limited repopulation of the irradiated tissues with ablative

radiation, bolstering its tumor-killing effects. Studies have shown that linear-quadratic model underestimates tumor control by SBRT [17], indicating that additional mechanisms may be at play in addition to DNA strand breaks and/or chromosome aberrations [18]. One of them may be significant vascular damage in tumors from SBRT, leading to indirect cell death [18][19]. In addition, Wang and colleagues demonstrated that ablative hypofractionated radiation therapy at ≥10 Gy per fraction enhances tumor-killing via preferential stimulation of necroptosis (i.e., programmed necrosis) [20]. In fact, a high expression of a key protein involved in activation of necroptosis (RIP3) is associated with improved local control and progression-free survival in patients with non-small cell lung cancer. Last but not least, recent studies have demonstrated an immuno-modulatory effect of ablative radiotherapy, which is a very active area of ongoing investigation. Using a 16-gene tumor inflammation signature, Kean et al. demonstrated that most localized PCa are “cold” (low immune activation state) tumors pre-HDRBT while HDRBT converted 80% of these “cold” tumors into an “intermediate” or “hot” tumor [21]. Radiation depending on the fraction size increases peptide repertoire, enhances MHC class I expression, and facilitates killing by cytotoxic T lymphocytes [22][23]. One area under intense research is the possible synergy between ablative radiation and immunotherapy [24].

However, it should also be noted that the advantage of a large fraction size of ablative radiation may potentially be partially offset by the hypoxic clonogens within the tumor. PCa ranks high among the malignancies in which hypoxia plays a major role in treatment resistance and metastases [25][26]. In fact, hypoxia-associated gene expression has been correlated with Gleason score [27] and early biochemical relapse after radiotherapy and local recurrence [28]. As the alpha/beta ratio of hypoxic tumor cells is higher [29], increasing the fraction size (for a similar, total, biologically effective dose (BED)) will only have a modest influence on the control of those tumors containing significant numbers of hypoxic clonogens [16].

3. SBRT as Monotherapy

The first patient receiving modern SBRT was treated in 2000 as part of a prospective single-arm trial based at the Virginia Mason Hospital [30]. Subsequently, SBRT was studied in a variety of prospective, single-institution and multi-institutional phase II trials. Concurrently to these studies of SBRT, a large non-inferiority randomized trial, the HYPO-RT-PC trial [9], was initiated in 2005 and compared a seven-fraction UHF-RT against CF-RT; the majority of patients were treated with older radiation techniques. Finally, in 2012, the PACE-B randomized trial comparing modern SBRT against modern MHF-RT and CF-RT was launched [10]. Long-term results from HYPO-RT-PC and pooled results from multiple single-arm phase II studies [11], as well as early results from PACE-B, were published in 2019, leading to SBRT becoming an accepted standard of care option in 2020 for low- and intermediate-risk prostate cancer. In this section, we will provide a detailed overview of selected prospective studies evaluating UHF-RT and specifically SBRT. The selected monotherapy series are summarized in Table 1.

3.1. Prospective Evidence

The HYPO-RT-PC trial [9] compared 5-year failure-free survival (FFS) rates between patients with intermediate- and high-risk disease treated with CF-RT or UHF-RT [9]. The trial, which enrolled 1200 men across 12 centers from 2005 to 2015, was powered to demonstrate the non-inferiority of UHF-RT. Androgen deprivation therapy (ADT) was not used with EBRT on either arm, although the study population was comprised of patients with intermediate-risk (89%) and high-risk (11%) disease. With a median follow-up time of 5 years, the 5-year FFS rates were 84% in both groups (adjusted hazard ratio 1.002 (95% CI 0.758−1.325; p = 0.99)). Acute patient-reported outcomes on the Prostate Cancer Symptom Scale (PCSS) urinary and bowel scales were significantly worse with UHF-RT at the end of treatment, with urinary scores remaining significantly worse three months later. A slight difference was notable one-year post-treatment for both urinary PCSS scores and physician-scored grade ≥ 2 genitourinary (GU) toxicity on the Radiotherapy Therapy Oncology Group (RTOG) scale. However, the 5-year cumulative incidence of grade ≥ 2 GU and gastrointestinal (GI) toxicities were similar in both arms. No differences in the preservation of erectile function were seen. Overall, these results confirmed the oncologic non-inferiority of UHF-RT compared with CF-RT, at least in the intermediate term, establishing UHF-RT as a valuable standard of care option for prostate cancer.

Importantly, the radiation planning technique used for 80% of patients was three-dimensional conformal radiotherapy, rather than the more modern intensity modulated radiotherapy (IMRT). The latter may be associated with lower absolute rates of toxicity [31]. Additionally, while 90% of patients had implanted fiducial markers to help track the target and thereby mitigate the impact of prostate motion between fractions, the planning margins used were 7 mm isotropically, which would be considered large by contemporary standards. Thus, the absolute rates of toxicity in both arms of the HYPO-RT-PC trial are likely higher than what would be expected with modern techniques.

Table 1. Selected recent stereotactic body radiation therapy (SBRT) monotherapy series in low- and intermediate-risk patients.

Author	Year	N	Risk	FU-Med	Dose/fx	Outcome (bRFS)	Toxicity	ADT
Widmark † (HYPO-RT-PC trial)	2019	598	89% I 11% H	5 years	42.7 Gy/7 fx (3 days per week)	5-year bRFS: 84%	Acute RTOG grade ≥ 2 GU toxicity: 28%, acute RTOG grade ≥ 2 GI toxicity: 24%. 5-year grade ≥ 2 GU toxicity: 18%, grade ≥ 2 GI toxicity: 10%, grade ≥ 3 GU toxicity: 4.2%, grade ≥ 3 GI toxicity: 1.7%.	No ADT allowed
Brand † (PACE-B trial)	2019	433	8% L 92% I	12 weeks	36.25 Gy/5 fx (7.25 Gy /fx delivered consecutively (20.7%) or over the span of ~2 weeks (79.3%))	n/a	Acute RTOG grade ≥ 2 GU toxicity exceeding baseline: 20.2%. Acute RTOG grade ≥ 2 GI toxicity: 9.3%.	No ADT allowed
Kishan	2019	2142	55.3% L 32.3% I (F) 12.4% I (UF)	6.9 years	33.5–40.0 Gy in 4 to 5 fx (88% 5 fx).	7-year bRFS: 95.5% L; 91.4% F-I; 85.1% UF-I, 89.8% for all I.	Acute grade ≥ 2 GU toxicity: 9.6%, grade ≥ 2 GI toxicity: 3.4%, grade ≥ 3 GU toxicity: 0.6%, grade ≥ 3 GI toxicity: 0.09%. 7-year cumulative incidence of late grade ≥ 3 GU toxicity: 2.4%, grade ≥ 3 GI toxicity: 0.4%.	5.4% received concurrent ADT; 3.6% for L, 9.4% for I (U)
Levin-Epstein	2020	1908	50.0% L 30.9% I (F) 19.1% I (UF)	6.0 years	35 Gy/5 fx 36.25 Gy/5 fx 40 Gy/5 fx 38 Gy/4 fx	93.8% 93.3% 96.1% 91.1%	n/a	Upfront ADT excluded

Zelefsky	2019	136	33.1% L 44.1% I (F) 22.8% I (UF)	5.9 years 5.4 years 4.1 years 3.5 years	32.5 Gy/5 fx 35 Gy/5 fx 37.5 Gy/5 fx 40 Gy/5 fx	5-year bRFS: 85%, 94%, 100%, 100%; 2-year positive biopsy post-RT: 47.6%, 19.2%, 16.7%, 7.7%	Acute grade 2 GI toxicities: 0%, 2.9%, 2.8%, and 11.4%; no grade 3+. Acute grade 2 GU toxicities: 16.7%, 22.9%, 8.3%, and 17.1%; no grade 3+. Late grade 2 GU toxicities: 23.3%, 25.7%, 27.8%, and 31.4%; 1 late grade 3 urinary toxicity (urethral stricture) developed in the 40-Gy dose arm; no grade 4.	Neoadjuvant ADT excluded

Risk groups: L/I/H: low-risk /intermediate-risk/ high-risk prostate cancer; F: favorable; UF: unfavorable; FU-med: median follow-up; bRFS: biochemical recurrence-free survival; ADT: androgen deprivation therapy; fx: fraction. † randomized controlled trial.

The PACE-B trial directly compared modern SBRT (36.25 Gy in five fractions of 7.25 Gy each; delivered consecutively or over the span of generally 2 weeks) with a control arm that allowed either CF-RT (78 Gy in 39 fractions of 2 Gy each; 31% of patients) or MHF-RT (62 Gy in 20 fractions of 3.1 Gy each; 69% of patients). This trial, which enrolled 874 men with low- and intermediate-risk PCa (Gleason 4 + 3 excluded) across 37 centers between 2012 and 2018, was designed to demonstrate the non-inferiority of SBRT with respect to freedom from biochemical or clinical failure at five years. The authors recently reported the results of a per-protocol, pre-specified substudy evaluating acute physician-scored toxicity on the RTOG scale [10]. The authors found that the cumulative rates of worst RTOG grade ≥ 2 GI toxicities exceeding baseline were 9.3% vs. 13.2% (SBRT vs. control arm), while for grade ≥ 2 GU toxicities, the rates were 20.2% vs. 26.8%. These typically occurred 4–6 weeks after the end of treatment, and by 12 weeks the rates dropped precipitously. No significant differences in GU or GI toxicities were identified at any timepoint by the RTOG scale. Similarly, no differences were found in the secondary endpoints of Expanded Prostate Cancer Index Composite (EPIC) bowel, urinary, and sexual bother, or worse acute grade ≥ 2 GU toxicity exceeding baseline on the Common Terminology Criteria for Adverse Events (CTCAE) scale. However, patients treated with SBRT did have significantly worse acute CTCAE grade ≥ 2 GI toxicity exceeding baseline (15.2% vs. 8%, $p = 0.011$), though this difference disappeared by 12 weeks. Overall, the PACE-B trial provides high-level evidence that the acute urinary and bowel outcomes with UHF-RT in HYPO-RT-PC may not be seen with more modern SBRT techniques.

Indeed, when directly comparing acute grade ≥ 2 RTOG GU toxicity rates, the rates were lower in PACE-B than HYPO-RT-PC (20.2% vs. 28%). This might be reflective of the use of IMRT and possibly reduced margins (4–5 mm isotropically, except 3–5 mm posteriorly). Further room for improvement may exist, however. Only 73% of patients treated with SBRT on PACE-B had implanted fiducial markers, and only 41.7% of patients had motion monitoring during treatment. Additionally, longer treatment intervals between SBRT fractions have been associated with decreased toxicity in prior studies [11][32] and an acute increase in physician-reported GI toxicity has been noted with moderate hypofractionation [8]. Daily fractionation was used for 20.7% of patients treated with SBRT on the PACE-B, and 69% of patients treated on the control arm received a moderately hypofractionated regimen. Thus, it may be important to dichotomize the control and experimental treatment arm by fractionation schedule, particularly when evaluating the impact of treatment time and fractionation for patients treated with SBRT. This will be critical in determining the optimal patients for treatment with SBRT. Of note, patients treated on HYPRO-RT-PC and PACE-B trials did not receive ADT; in the former case, this was due to lack of information regarding the importance of ADT at the time of trial design, while in the latter case it was due to the overall favorable risk nature of patients enrolled on the study.

The longest-term outcome data for modern SBRT comes from a pooled consortium study that included data from 12 single-arm phase II studies that together enrolled 2142 patients between 2000–2012 [11]. The median follow-up was 6.9 years. The trials generally enrolled patients with low-risk (55.3%) and favorable intermediate-risk disease (32.3%), though

a minority had unfavorable intermediate-risk disease (12.4%). ADT was used in a minority of patients. Regimens ranged from 38 Gy in four fractions of 9.5 Gy each to 40 Gy in five fractions of 8 Gy each. The cumulative incidences of late grade ≥ 3 or higher toxic events by either RTOG or CTCAE scales (as defined by the individual studies included) were evaluated based on central review. With a median follow-up of 6.9 years, the seven-year cumulative incidence of late grade ≥ 3 GU toxicities was 2.4%, and the rate of grade ≥ 3 GI toxicities was 0.4%. The seven-year cumulative incidence biochemical recurrence was 4.5% for low-risk disease, 8.6% for favorable intermediate-risk disease, and 14.9% for unfavorable intermediate-risk disease. This compares favorably to the Conventional Versus Hypofractionated High-Dose Intensity Modulated Radiation Therapy for Prostate Cancer (CHHiP) trial, which demonstrated that 4 weeks of hypofractionated RT (HF-RT) was non-inferior regarding BCR and toxicity compared with 8 weeks of CF-RT. In the CHHiP trial, 8-year biochemical recurrence-free survival (bRFS) for men with low-, intermediate-, and high-risk disease was as 83.7% (comprised of 15% low-, 73% intermediate-, and 12% high-risk patients) [33], compared with 7-year bRFS rates of 95.5% and 89.9% with SBRT for low- and intermediate-risk disease in the consortium study. In the CHHiP trial, 97% of participants received 4–6 months of ADT via either medical castration or a direct anti-androgen [34]. These results are consistent with a systematic review and study-level meta-analysis [12], which reports a 5- and 7-year bRFS rates of 95.3% and 93.7%, respectively, with favorable toxicity profile, in a cohort of patients with low-, intermediate- and high-risk patients. In both the pooled SBRT consortium [11] and the meta-analysis [12], ADT use was not significantly associated with bRFS, though such analyses were likely underpowered and susceptible to selection biases.

Though not randomized evidence, this report provides prospectively collected multi-institutional data in a large cohort of patients treated with SBRT. Of note, the patients included in this report received treatments with protocols most reflective of modern SBRT delivery, with tighter margins (2–5mm isotropically), 100% implanted fiducial markers and 88% real-time motion management during treatment. Indeed, the low absolute rates of grade ≥ 3 toxicity seen at seven years (over three-fold less than in the HYPO-RT-PC trial) may be secondary to these technological improvements.

3.2. SBRT Dose

As the evidence supporting SBRT as a standard of care monotherapy option has grown, further questions involving the technical aspects of treatments, such as dose and fractionation, have emerged. While a comprehensive overview of all studies is beyond the scope of this study, we will briefly review the emerging data regarding SBRT dosing and fractionation.

The fundamental premise behind dose-escalation is that locally recurrent or persistent disease may ultimately seed distant metastases. As such, dose escalation efforts are geared to optimize local control, but may not directly address micrometastatic regional or distant disease that exists on presentation. It is generally acknowledged that, particularly for aggressive disease, metastatic failure may be a more common mode of relapse; however, local relapse precedes a large proportion of metastatic failures at longer-term follow-up [35][36]. Dose escalation has been widely studied in the context of CF-RT. Of the multiple randomized trials that have been published, only one suggested an improvement in prostate cancer-specific survival [37], and only two suggested an improvement in the incidence of metastasis [38][39]. Nearly all studies have, however, shown an improvement in biochemical control with dose-escalation—albeit at the cost of increased GI, if not also GU, toxicity.

If we assume that the alpha/beta ratio of prostate cancer is indeed low (on the order of 2–3), an SBRT dose of 36.25 Gy in five fractions would have an equivalent dose in 2-Gy fractions (EQD2) ranging from 74.3–83.8 Gy. Thus, this dose would be roughly commensurate with modern, dose-escalated CF-RT, and no randomized trials have evaluated doses in the context of UHF-RT. The aforementioned study-level meta-analysis found that increasing BED was significantly associated with improved bRFS [12]. In contrast, a subset analysis of the pooled SBRT consortium failed to reveal an association between EQD_2 and time to BCR for any risk group [11]. A detailed comparison of bRFS in 1908 patients after 35 Gy/ five fractions, 36.25 Gy/ five fractions, 40 Gy/ five fractions, and 38 Gy/ four fractions found a difference in prostate ablation, without a clear difference in bRFS at 5-years [40]. However, at a median follow-up of 72.3 months, treatment with 40 Gy/ five fractions was associated with improved long-term bRFS when compared against all other doses. The decoupling of prostate tumor ablation and bRFS between 38 Gy/ four fractions and 40 Gy/ five fractions could be explained by extraprostatic failures presenting a dominant pattern of failure after SBRT at this dose level, though the lack of a significant difference between 38 Gy/ four fractions and lower SBRT doses is more difficult to explain. The general finding of increased local control/prostate tumor ablation by escalating dose up to 40 Gy is in accordance with the results of a prospective dose-escalation trial from Memorial Sloan Kettering Cancer Center (MSKCC) of 136 patients who received SBRT at doses ranging from 32.5 Gy/ five fractions to 40 Gy/ five fractions [41]. In that trial, significantly fewer positive biopsies were seen two years after radiotherapy with escalating dose. Improved PSA response with 40 Gy/ five fractions

vs. 35 Gy/ five fractions was also seen in a comparison of two single-arm prospective studies, although no difference in bRFS was found [42]. A plateau to the dose response was also suggested by a recent modeling study [43]. It is acknowledged that there are few data exploring doses above 40 Gy applied with UHF-RT [44][45].

Given the unclear benefit for dose escalation above 40 Gy, the cost must be considered. In one study comparing two prospective five-fraction SBRT studies of 40 vs. 35 Gy [46], patients receiving 40-Gy SBRT experienced greater grade ≥ 2 cumulative GU (24.2% vs. 5%) and GI (26.2% vs. 7.6%) toxicities by the RTOG scale compared to those receiving 35-Gy. Notably, the 40-Gy arm also utilized larger PTV margins (5 vs. 4 mm). In the aforementioned prospective MSKCC study [41], the 40-Gy dose cohort had significantly higher International Prostate Symptom Score (IPSS) scores at 12 months compared to lower dose cohorts. At 24 months, however, the increase in IPSS was only marginally significant compared to the 32.5-Gy group but not others. Finally, at 36 months no significant differences were observed across the various dose cohorts. An overall decrease in erectile function was also seen at 24 months across the board with no significant difference among different dose levels. Taken together, the results suggest that dose escalation may be associated with worse physician-scored toxicity and IPSS, though the effect on IPSS dissipates within 3 years.

3.3. SBRT Fractionation

The earliest studies of prostate SBRT treated patients on consecutive days (QD) [30][47]. Early results from the initial cohort of patients treated on the Stanford trial demonstrated an unexpectedly high rate of grade ≥ 2 rectal toxicity, motivating an every-other-day (QOD) schedule. Specifically, 0% vs. 38% of patients reported “moderate” or “big problem” in terms of rectal quality of life with QOD vs. QD fractionation [47]. Subsequently, treating QOD became the *de facto* standard in many studies. A subset analysis of the pooled SBRT consortium showed that QOD treatment was associated with lower odds of acute grade ≥ 2 toxicity than QD fractionation [11]. The PATRIOT trial [32] randomized patients to 40 Gy in five fractions delivered once weekly (QW) or QOD and demonstrated superior acute bowel and urinary QOL with QW treatments. At a median follow-up of 62 months [48], no differences in late toxicity, QOL, BCR were noted, although more patients on the QW arm received salvage ADT (0 vs. four patients). Two-fraction and single-fraction SBRT have been studied in the TWOSTAR and ONE SHOT trials, respectively; longer-term follow-up is awaited for both [49][50].

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