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Moderate hypofractionation and stereotactic body radiation therapy in the treatment of prostate cancer

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Abstract

For prostate cancer radiation therapy, daily sessions spanning approximately 2 months has been considered the standard of care for patients managed with curative intent. In recent years, data has emerged which supports the use of higher dose per fraction schemes leading to a reduced duration of treatment. This form of radiation—generally termed moderate hypofractionation or stereotactic body radiation therapy—increasingly appears to be a safe and effective alternative to the conventional course. This review summarizes salient data from the literature on outcomes, toxicities, and future directions for this innovative strategy of care.

Keywords: Prostate cancer; Radiation therapy; Hypofractionation; SBRT; SABR

1. Introduction

External beam radiotherapy for prostate cancer has changed greatly over the past 2 decades. Up until at least the 1990s, standard radiation courses were 60 to 64 Gy in 1.8 to 2.0 Gy fractions [1]. However, it was (and is) widely acknowledged that the higher dose of radiation which can be safely delivered, the higher the probability of tumor control. As time has progressed, dose escalation studies have brought conventional fractionation regimens to 74 to 80 Gy using 1.8 to 2.0 Gy fractions, which has been shown to achieve greater biochemical disease control when compared to 64 to 70.2 Gy [2–7].

Given the radiobiological understanding of prostate cancer radiation dose response to larger fraction sizes, as well as the prolonged treatment course required to deliver modern doses of external beam radiotherapy, individual institutions and cooperative groups developed an interest in using larger fraction sizes for treatment. As a result, 2 basic schools of larger-than-conventional fraction sizes have been investigated: moderate hypofractionation, encompassing doses of 2.2 to 4 Gy per fraction [8], and stereotactic body radiotherapy (SBRT) (otherwise known as "extreme hypofractionation," "aggressive hypofractionation," or "stereotactic ablative body radiotherapy"), typically encompassing doses of 3.5 to 15 Gy per fraction [9]. Large clinical trials subsequently have matured for moderate hypofractionation, including CHHiP, RTOG 0415, PROFIT, and HYPRO (discussed below). For SBRT, data comes from retrospective and prospective studies rather than randomized clinical trials, with the exception to this being the randomized phase II trial RTOG 0938 and the Hypofractionated Radiotherapy of Intermediate Risk Localized Prostate Cancer trial.

A discussion of the relative benefits of hypofractionation in the United States would be incomplete without a discussion of the relatively lower cost of hypofractionation compared to standard fractionation for prostate cancer. The incorporation of new radiation oncology technologies—such as magnetic resonance imaging (MRI)-guided therapy—will be briefly discussed.

2. Radiobiology

The underpinning of the success (or failure) of various fractionation strategies rests in the biological response to

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ionizing radiation exposure. In the laboratory, classic experiments with colony forming assays and the resultant cell survival curves catalyzed the development of the linear-quadratic model and the alpha/beta ratio. The alpha/beta ratio can be used to succinctly communicate a cell type's sensitivity or resistance to radiation. The creation of "conventional" fractionation of 1.8 to 2.0 Gy is born out of this ratio. Speaking very broadly, most malignant tissues have high alpha/beta ratios (~10) whereas most normal tissues have low ratios (~3), that, when applied to this model, indicates a greater cell kill of malignancy at lower doses per fraction.

Prostate adenocarcinoma is a notable exception to this generality; it is broadly accepted to have a lower alpha/beta ratio of 1.5 to 3.0 [10]. Logically then, if a lower dose per fraction is more effective for high-ratio tissues, a higher dose per fraction would be more effective for low-ratio tissues.

The combination of these 2 factors—low alpha/beta ratio and the potential for better control with higher doses—led clinicians to push toward increasingly shorter treatment courses. Whether the therapeutic ratio is improved with hypofractionation, however, depends on the "alpha/beta of toxicity." Measuring the response of normal tissue to radiation with regards to toxicity is an extremely complex and multifactorial undertaking [11]. Therefore, ultimately understanding the relative risks and benefits of hypofractionated radiotherapy will depend on the long-term outcomes of clinical trials.

3. Moderate hypofractionation

One of the first studies to examine the feasibility of hypofractionation was published in 1991 out of the St. Thomas Hospital in London [12]. More than 200 patients who were treated between 1962 and 1984 with external beam radiation therapy (EBRT) were studied. The treatment scheme (which was motivated by efficient use of scarce resources) used 55 Gy in 12 fractions initially, then 36 Gy in 6 fractions over 3 weeks. Given the era of this study, the outcome metrics utilized are not directly comparable to what is currently standard. However, cancer mortality from the treated patients was 69% at 5 years and 33% at 10 years, with a median survival of 8.1 years. Of the 111 patients still alive at the data analysis cutoff point (October 1986), 28.8% required additional treatment for disease progression. No official grading scale was used to assess morbidity, but the study authors note that, in terms of early effects, "...the majority of patients developed some frequency of micturition and tenesmus, which settled within a period of 2 to 3 weeks." Regarding late effects, 2 patients developed rectal strictures. Erectile function was not assessed, and the authors report that no secondary malignancies developed within the irradiated field.

In 2007 Kupelian et al. published results from the Cleveland Clinic looking at 770 patients between 1998 and 2004, with a median follow-up of 45 months [13]. They utilized 70 Gy in 2.5 Gy fractions over 5 weeks. At 5 years, biochemical recurrence-free survival was 82% (patients were 95% low risk, 85% intermediate risk, and 68% high risk). Toxicity was comparable to conventional fractionation.

In 2013, Pollack et al. published a randomized trial comparing hypofractionated EBRT to conventional courses of therapy. More than 300 men with favorable- to high-risk prostate cancer received either intensity modulated radiotherapy (IMRT) consisting of 76 Gy in 38 fractions or a hypofractionated regimen of 70.2 Gy in 26 fractions [14]. With a median follow-up of 5.5 years, this study sought to compare the relative efficacy of each regimen in prevent biochemical and/or clinical recurrence. Their results demonstrated no significant difference in disease-free survival (21.4% at 5 years for conventional vs. 23.3% for hypofractionated) and, in general, the toxicity profile was similar. Grade 2 or above GU toxicity was reported in 47.7% of conventionally treated patients compared to 44.9% in the hypofractionated group. Grade 2 or above GI toxicity was reported in 22.5% vs. 18.1% of patients, respectively. Notably, the men who—at the outset of treatment—had worse baseline urinary function had significantly worse obstructive symptoms after completing the hypofractionated treatment.

A study from MD Anderson examining over 200 patients showed an absolute benefit of 4.7% in recurrence with a median follow-up of 8.4 years when comparing 72 Gy in 30 fractions vs. 75.6 Gy in 42 fractions [15]. Additionally, the Dutch HYPRO trial took 820 patients (intermediate- or high-risk) and treated them with either 64.6 Gy in 19 fractions or 78 Gy in 39 fractions [16]. Although there was a trend favoring the shorter treatment course, the hazard ratio was not significant, and the study could not demonstrate noninferiority. Additional analysis of the HYPRO trial found that both acute and late patient-reported toxicities could not be demonstrated to be noninferior to standard fractionation [17,18]. Of note, cumulative incidence of at least Grade 2 acute GI toxicity was significantly worse for the hypofractionated arm.

In 2017, a group of Italian researchers published the results of a randomized trial comparing conventional and hypofractionated radiotherapy in high-risk patients [19]. A total of 168 patients were assigned to either 80 Gy in 40 fractions or 62 Gy in 20 fractions, targeting the prostate and seminal vesicles. With a median follow-up of 9 years, there was no significant difference in physician-assessed late GU or GI toxicities greater than, or equal to, Grade 2. Additionally, while there was a trend favoring freedom from biochemical failure and overall survival in the hypofractionation group, there was no statistically significant difference in either metric. Furthermore, there was some concern raised by the higher rate of macroscopic hematuria seen in the hypofractionated arm (Yu, 2017). In their conclusion, however, the authors note that a "postrandomization hypothesis-generating analysis revealed an association between the use of hypofractionation and a decreased risk of death from

Table 1
Moderate hypofractionation noninferiority RCTs.

Trial	Risk group	Patients enrolled	Median follow-up (years)	ADT	Dose and fractions	~5 Year control	Late GI toxicity (≥G2)	Late GU toxicity (≥G2)
RTOG 0415	Low risk	1,115	5.8	0%	73.8 Gy 39 fx	**85.4%**	14%	22.8%
					70 Gy 28 fx	**86.3%**	22.4%	29.7%
CHHiP	Low Intermediate High	3,216	5.1	>95%	74 Gy 37 fx	**88.3%**	13.7%	9.1%
					60 Gy 20 fx	**90.6%**	11.9%	11.7%
					57 Gy 19 fx	**85.6%**	11.3%	6.6%
PROFIT	Intermediate	1,205	6	<5%	78 Gy 39 fx	**85%**	13.9%	22%
					60 Gy 20 fx	**85%**	8.9%	22.2%
HYPRO	Intermediate High	820	5	67%	78 Gy 39 fx	**77.1%**	17.7%	39.0%
					64.6 Gy 19 fx	**80.5%**	21.9%	41.3%

(prostate cancer), which adds to the logistical and economic advantages of fewer numbers of fractions."

Three large trials were powered to examine the noninferiority of hypofractionation compared to conventional treatment (see Table 1). All 3 had a median follow-up of 5 to 6 years and looked at low-, intermediate-, and high-risk patients. RTOG 0415, studying low-risk patients, used either 73.8 Gy in 39 fractions or 70 Gy in 28 fractions, showing similar (~85%–86%) 5-year control rates [20]. The 28 fraction arm did see higher Grade 2 through Grade 4 late GI and GU toxicity (~7% increase for each in the hypofraction arm compared to conventional fractionation) [20]. The PROFIT trial, studying intermediate risk patients, used either 78 Gy in 39 fractions or 60 Gy in 20 fractions, and also showed similar 5-year control rates. Compared to RTOG 0415, GI and GU toxicities were comparable [21]. Finally, the CHHiP trial (using low-, intermediate-, and high-risk patients) utilized concurrent Androgen deprivation therapy for 6 to 9 months [22]. Three different fractionation schemes were employed: 74 Gy in 37 fractions, 60 Gy in 20 fractions, and 57 Gy in 19 fractions. Compared to the conventional fractionation arm, the 2 hypofractionation arms were demonstrated to be noninferior and all 3 arms had relatively similar 5-year control rates (85.9%–90.6%), though the 57 Gy arm could not be excluded as noninferior. Interestingly, the 57 Gy arm also had almost half the rate of Grade 2 through Grade 4 GU toxicity (6.6% vs. 11.7%).

4. ASTRO guidelines on moderate hypofractionation

When considered in total, the body of work investigating the safety and efficacy of moderate hypofractionation vs. conventional fractionation in the treatment of prostate cancer strongly supports its equivalence in terms of outcomes with the added benefits of decreased costs and increased patient convenience. Accordingly, in November of 2018, the American Society for Radiation Oncology (ASTRO) published guidelines on the use of hypofractionated radiation therapy in the treatment of prostate cancer in conjunction with the American Society of Clinical Oncology and the American Urological Association [23]. For men who are candidates and opt to receive radiation therapy, the ASTRO task force now strongly recommends that moderate hypofractionation be offered to low-, intermediate-, and high-risk patients. Given that there have been no head-to-head trials to discern the optimal treatment course, the task force recommends using either 60 Gy in 20 fractions or 70 Gy in 28 fractions as these 2 regimens have the most robust literature support. They also recommend the use of image-guided radiation therapy (whereby setup verification imaging is performed on the linac) and the avoidance of less modern methods such as nonmodulated 3-D conformal radiotherapy.

5. SBRT

Taking the advantages of hypofractionation to the extreme, SBRT delivers high doses of radiation to the prostate in 5 or fewer total treatments. Dose per fraction is typically ≥5 Gy with total doses spanning 30 to 50 Gy [9,23]. Though not considered SBRT in the modern sense, "extreme" hypofractionated therapy was first published in the 1960s, where 232 patients were treated with 6 fractions of 6 Gy each over a span of 18 days. Though somewhat

Table 2
Moderate hypofractionation superiority RCTs.

Trial	Risk group	Patients enrolled	Median follow-up (years)	ADT	Dose and fractions	Disease control	Late GI toxicity (≥G2)	Late GU toxicity (≥G2)
Lukka et al.	N/A	938	5.7	0%	66 Gy 30 fx	**52.95%**	No difference	No difference
					52.5 Gy 20 fx	**59.95**		
Yeoh et al.	N/A	217	7.5	0%	64 Gy 32 fx	**34%**	No difference	No difference
					55 Gy 20 fx	**53%**		
Arcangeli et al.	High	168	9	100%	80 Gy 40 fx	**65% (10 years)**	15.4%	21%
					62 Gy 20 fx	**72% (10 years)**	13.5%	14%
Pollack et al.	Intermediate High	303	5.7	20%–int. 100%–high	76 Gy 38 fx	**21.4%**	22.5%	14.6%
					70.2 Gy 26 fx	**23.3%**	18.1%	15.3%
Hoffman et al.	Low Intermediate	206	8.4	24%	75.6 Gy 42 fx	**84.6%**	5%	16%
					72 Gy 30 fx	**89.3%**	13%	15%

surprising, the 232 patients included in the analysis showed relatively low morbidity and a 10-year overall survival of at least 50% [12]. The experimentation with this approach was more due to an economic, as opposed to a technologic, rationale and did not gain popular traction at the time. It was not until the 2000s, and the consummate advances in radiation treatment planning and delivery, that SBRT of prostate cancer took off.

SBRT permits the attainment of advantages of brachytherapy—namely, steep dose gradients—without falling prey to some of its drawbacks, such as the acquisition of specialized devices and equipment and the risks inherent to any surgical procedure.

As the technology used to deliver SBRT to the prostate is still relatively young, so too is the data supporting its use. However, data are rapidly maturing. While it may be premature to make conclusive claims about SBRT, much of the trials show very promising outcomes in terms of biochemical control and toxicity. Tables 2 and 3 summarize 16 retrospective and prospective trials.

The first of these trials took 40 patients with early-stage disease and treated them with 5 Linac-based fractions of 6.7 Gy [24]. With a median 41 months of follow-up, 90% of patients showed no evidence of disease and no Grade 3 complications were reported.

Two additional Linac-based studies were published in 2013. One looked at 50 low- and intermediate-risk patients treated to 38 Gy in 4 fractions and found a 100% disease-free survival at a median of 23 months [25]. The second examined 84 low-risk patients treated to 35 Gy in 5 fractions, demonstrating an impressive 98% disease-free survival (DFS) at a median of 55 months [26].

Much of the foundational data regarding SBRT in prostate cancer comes from the CyberKnife system (Accuray Incorporated, Sunnyvale, CA). Compared to a standard linear accelerator, the CyberKnife consists of a lightweight linac fixed to a mobile robotic module with real-time onboard imaging. This allows the machine to adjust radiation delivery during treatment with the aim of minimizing normal tissue toxicity and maximizing treatment efficacy. The earliest report from 2012 took 67 low-risk patients and treated them to 36.25 Gy in 5 fractions [27]. At 4 years, overall freedom from biochemical recurrence was 94%. There was no reported Grade 3 or above GI toxicity and only 3% of patients experienced Grade 3 or above GU toxicity. Interestingly—though not necessarily surprising—fewer incidences of low-grade toxicity was reported in patients who received alternating (day on, day off) vs. consecutive treatments. A total of 50% of patients treated with daily fractionation reported Grade 1 GU toxicity as compared to 12% of patients treated every other day, and 37% of the patients treated daily reported Grade 1 GI toxicity compared to just 5% of patients treated on alternating days.

Three studies were published in 2013 describing the experiences of treating low-, intermediate-, and high-risk patients [28–30]. Therapeutic regimens utilized ranged from 35 to 37.5 Gy, all delivered in 5 fractions. With median follow-up periods ranging from 27.6 to 36 months, low- and intermediate-risk patients had a freedom from

Table 3
SBRT studies (with at least 40 patients).

Citation	Risk group	#Patients	Study type	Median follow-up (months)	Dose/fractions	ADT	Disease control	GI toxicity (≥G2)	GU toxicity (≥G2)
D'Alimonte	Low	84	Prospective	50	35 Gy/5 fx	N/A	**98%**	1%	1%
Loblaw	Low	84	Prospective	55	35 Gy/5 fx	1%	**98%**	7%	5%
Menkarios	Low	80	Prospective	33	45 Gy/5 fx	N/A	**97%**	16%	14%
Ouon	Low	84	Prospective	18	35 Gy/5 fx	N/A	**N/A**	5%	2%
Bolzicco	Low Intermediate High	100	Prospective	36	35 Gy/5 fx	29%	**96%**	1%	4%
Chen	Low Intermediate High	100	Retrospective	28	35–36.25 Gy/5 fx	11%	**99%**	1%	31%
Katz	Low Intermediate High	515	Prospective	54	35–36.25 Gy/5 fx	19%	**97%–low** **92%–int** **70%–high**	4%	9%
King	Low	67	Prospective	32	36.25 Gy/5 fx	N/A	**94%**	12%	7%

biochemical recurrence rate of 95% to 100%, while 1 study noted a 77.1% rate for high-risk patients [30]. Reported Grade 3 to 4 early and late toxicities were generally very low, ranging from 0% to 4%.

A pooled analysis of prospective phase II SBRT data examined 1,100 patients across 8 centers from 2003 to 2011 was published in 2013 [31]. Low-, intermediate-, and high-risk patients received 36.25 Gy in 4 to 5 fractions. Androgen deprivation therapy was used in 14% of men. At 5 years, the biochemical control rate was 93% for all patients. Stratified into risk groups, the 5-year control rate was 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively. Toxicity data for a subset of patients ($n = 864$) was published in separate report and utilized the "Expanded Prostate Cancer Index Composite (EPIC) instrument" [32]. Median follow-up was 3 years with 194 patients remaining evaluable at 5 years. Based on the EPIC questionnaire, patients reported a temporary decline in urinary and bowel function within the first 3 months post-treatment which returned to baseline status (or better) within 6 months. This improvement in treatment toxicity was sustained beyond 5 years.

Fuller et al. used 38 Gy in 4 fractions to treat 79 low- and intermediate-risk patients [33]. This study is particularly notable as it sought to mimic the highly conformal dose distribution normally achieved only through high-dose-rate brachytherapy procedures. Their hypothesis was that the technology of the CyberKnife system would enable clinicians to attain the benefits of brachytherapy (more precise dose sculpting, quicker treatment time) while avoiding some of the inherent drawbacks (invasive procedure with risk of bleeding/infection, hospital admission, pain, etc.). At 42 months of follow-up, 100% of the low-risk and 92% of the intermediate-risk patients experienced freedom from

Table 4
SBRT studies (with at least 40 patients).

Citation	Risk group	# Patients	Study type	Median follow-up (months)	Dose/ fractions	ADT	Disease control	GI toxicity (≥G2)	GU toxicity (≥G2)
Meier	Intermediate	129	Prospective	30	40 Gy/5 fx	N/A	**99%**	2%	10%
Aluwini	Low Intermediate	162	Prospective	28	38 Gy/4 fx	N/A	**98%**	3%	15%
Fuller	Low Intermediate	260	Prospective	20	38 Gy/4 fx	N/A	**98%**	0%	2%
Freeman	Low	41	Prospective	60	35–36.25 Gy/5 fx	N/A	**N/A**	2.5%	9.5%
Madsen	Low	40	Prospective	41	33.5 Gy/5 fx	N/A	**90%**	13%	23%
McBride	Low	45	Prospective	44.5	36.25–37.5 Gy/ 5 fx	N/A	**100%**	27%	19%
Oliai	Low Intermediate High	70	Retrospective	31	35–37 Gy/5 fx	33%	**100%–low** **95%–int.** **77.1%–high**	12%	23%
Hannan	Low Intermediate	91	Prospective	74 (45 Gy) 72 (47.5 Gy) 66 (50 Gy)	45–50 Gy/5 fx	16.5%	**100%–3 years** **98.6%–5 years**	6.7%–45 Gy 26.7%–47.5 Gy 23%–50 Gy	33.3%–45 Gy 6.7%–47.5 Gy 23%–50 Gy

biochemical recurrence. Impressively, median pre-SBRT prostate-specific antigen (PSA) levels of 5.6 ng/ml decreased to 0.05 ng/ml at 5 years and 0.02 ng/ml at 6 years. Acute and late Grade 2 GU toxicity incidence was 10% and 9% (low-risk and intermediate-risk, respectively). No acute Grade 3 or above GU or GI toxicities were described, though 6% of patients reported late Grade 3 or above GU toxicities. While these toxicity rates are slightly higher as compared to other SBRT studies, they can likely be attributed to the specific dose prescribing technique employed by the investigators.

In 2015 Meier et al. looked at 137 intermediate-risk patients treated with 40 Gy in 5 fractions [34]. A total of 95% of patients were free of biochemical recurrence at 56 months. Toxicity rates were generally very low, with only 1.5% of patients reporting at least Grade 3 GI toxicity.

Also presented in 2015 was a paper from the PROSTQA Study Consortium comparing patient-reported quality of life after treatment with SBRT, conventional fractionation, or brachytherapy [35]. A total of 803 patients were included in an analysis which examined quality of life scores from baseline to 2 years post-treatment. Compared to conventional treatment, men treated with SBRT reported similar urinary and sexual side effects but noted significantly less bowel toxicity.

Katz et al. treated 515 men with low-, intermediate-, and high-risk to disease to 35 to 36.25 Gy in 5 fractions [36]. With a median of 84 months of follow-up, disease-free survival was 93.6% for low-risk patients, 84.3% for intermediate-risk, and 65% for those with high-risk disease. Published in a separate report [37], fewer than 5% of patients had any Grade 2 or above acute GI or GU toxicities. Late ≥Grade 2 GU toxicities occurred in 18% of patients and ≥Grade 2 GI toxicities were reported in 7.7% of patients.

The Hypofractionated Radiotherapy of Intermediate Risk Localized Prostate Cancer study [11] reported that an "ultrahypofractionated" regimen of 6.1 Gy × 7 fractions given every other day had a similar side effect profile to conventional 2.0 Gy × 39 fractions with 2 years of follow-up [38]. Of note, investigators utilized older 3-dimensional conformal planning techniques in this study. In a 2018 abstract update, they reported that 83.8% vs. 83.7% of patients treated with standard radiotherapy and ultrahypofractionated radiotherapy, respectively, had no signs of recurrence at 5-year follow-up [39]. Long-term side effects were the same between regimens, and they continue to follow this cohort to look for longer term side effects and differences in survival.

A single-arm prospective phase II trial utilizing 38 Gy in 4 fractions published results in the summer of 2018 [40]. Investigators enrolled 259 low- or intermediate-risk patients from 2007 to 2012. Of note, radiation treatment planning was performed in a brachytherapy-mimic fashion, similar to the previously discussed study published in 2014. Five-year biochemical control rates were 100% and 88.5% for low- and intermediate-risk patients, respectively. The cumulative ≥Grade 2 GU toxicity rate was 14.7% and only 3.4% for ≥Grade 2 GI toxicities. The median PSA of 5.12 ng/ml decreased to 0.1 ng/ml by 42 months, which the authors interpret as indicating prostatic ablation.

Very recently, a report was published on 5-year outcomes of the largest multi-institutional prospective trial of SBRT [41]. A total of 21 sites participated (including community and academic practices). Importantly, initial treatment plans underwent centralized review to ensure quality and consistency. The study stratified patients into 2 groups: low risk (172 patients) and intermediate risk (137 patients) based on standard prognostic factors ("T" stage, Gleason score, PSA). The dose prescription was 40 Gy in 5 fractions to the prostate (36.25 Gy to the planning target volume (PTV)). The PTV expansion was nonuniform and included 2 cm of the seminal vesicles in the intermediate-risk group (the vesicles were not intentionally targeted in the low-risk group). Also importantly, androgen deprivation therapy was not permitted during or after radiation. For all treated patients (both low and intermediate risk), the 5-year overall survival was 95.6% and the freedom from biochemical recurrence was 97.1%. In terms of toxicity, no Grade 4 or 5 events occurred. Grade 3 toxicities were reported in 1.2% of the low-risk patients and 1.5% of the intermediate-risk patients. The study authors conclude that their data on disease control and observed toxicity make SBRT a suitable option for select low and intermediate-risk patients.

Also recently published were the patient-reported outcomes from RTOG 0938, which utilized 2 "ultrahypofractionated" regimens for prostate cancer [42]. Patients were assigned to either 36.25 Gy in 5 fractions or 51.6 Gy in 12 fractions. In this study, the previously discussed EPIC instrument was utilized to measure toxicity. Lukka et al. created a noninferior study design to demonstrate that toxicity which occurred during ultrahypofractionated treatment was not significantly worse compared to patients receiving standard radiation courses. With a median follow-up of 3.8 years, they found that the urinary and rectal quality of life outcomes were comparable to patients who underwent the longer, conventionally fractionated regimens.

Finally, a Medicare claim-based analysis of patients treated from 2008 to 2011 found that SBRT was associated with a higher rate of claims indicative of urinary toxicity compared to IMRT (odds ratio 1.38; 95% confidence intervals 1.12−1.64; $P = 0.001$) within 24 months of treatment. The increase in claims was largely due to increases in claims for the evaluation and treatment of urethritis, urinary incontinence, and/or urinary obstruction [43]. These findings have been validated by other analysis of Medicare [44] and insurance claims [45].

6. Moderate hypofractionation vs. SBRT

There has only been 1 study (of which we are aware) that has compared moderate hypofractionation schemes to SBRT in terms of side-effect profiles. Pooling data from several institutions, Johnson et al. examined 378 men who received moderate hypofractionation therapy and compared them to over 500

men who received SBRT [46]. Moderate hypofractionation, in this case, was defined as <5 Gy/fraction, whereas SBRT was defined as 5 to 10 Gy/fraction. At 1 year, the hypofractionation patients were more likely to experience more worsening bowel symptoms compared to SBRT patients, and this gap widened at 2 years. This was also observed for urinary symptoms but to a more significant degree. Sexual side effects were relatively similar between the 2 groups.

There are ongoing randomized phase III studies comparing SBRT to moderate hypofractionation. The Miami Hypofractionation via Extended vs. Accelerated Therapy for Prostate Cancer trial (using a noninferior design) compares 36.25 Gy delivered in 5 fractions to 70.2 Gy given in 26 fractions [47]. The trial is estimated to complete in 2023. Additionally, the NRG GU-005 trial (randomized, phase III) seeks to demonstrate that SBRT will actually prove superior to moderate hypofractionation in terms of patient-reported toxicity [48]. Additional measures will include biochemical failure, overall survival, local failure, prostate cancer-specific survival, and distant metastases. GU-005 is projected to close to accrual in 2021, and report findings by 2025.

7. Costs

The 7 to 9 weeks of once-daily radiation sessions can be a tedious, exhausting experience for patients with prostate cancer. Shifting the standard of care toward a shorter treatment course has the potential to decrease the burdens of cost, energy, and stress to both the patient and the healthcare system as a whole. Theoretically, increasing the dose per fraction has been projected to decrease the total number of required treatment fractions by over 200,000 per year [22]. Konski et al. calculated that this change equates to savings of $9,041 per patient [49].

One study estimated the mean cost of SBRT at $22,152, as compared to $35,431 for patients treated with conventional IMRT [50]. Similarly, for Medicare patients, the mean cost of treatment is estimated to be $13,645 for SBRT compared to $21,023 for IMRT [43]. A third manuscript stratified the cost of multiple treatment options, demonstrating that arc-based SBRT, with an estimated cost of $4,368/patient, is most cost effective when compared to fixed gantry treatment ($4,443/patient), robotic-based radiosurgery ($6,333/patient), arc-based conventional-fraction IMRT ($5,935/patient), and fixed gantry conventional-fraction IMRT ($7,992/patient) [51].

Kothari et al. [52] postulated that cost savings go beyond savings to the hospital, as it decreases costs that are directly absorbed by the patients due to time off work, transport, and parking. They predict an average hypothetical savings of $5,517 in direct patient costs [53].

8. Future directions

Using such large doses-per-fraction of radiation requires accurate imaging and target delineation to facilitate both safety and disease control. As imaging technology progresses, advancing beyond computed tomography-based manual contouring becomes more reasonable and potentially cost-effective. Pathmanthan et al. describe that extreme hypofractionation can be possible through autosegmentation (software delineating anatomical volumes as opposed to a clinician), MRI-only workflow (where treatment planning is done without an additional computed tomography scan), and real-time adaptive replanning (modifying dose delivery based on the natural motion of internal targets and avoidance structures during treatment) [54]. Another potential benefit of MR-guided treatment could be the ability to use sequential MRI to account for intertreatment prostate size changes due to swelling of the gland [55].

Another area of innovation is the use of an SBRT boost, and there have been a handful of studies/trials investigating this possibility. The largest trial out of Georgetown examined 108 patients and utilized 19.5 Gy in 3 fractions followed by standard external beam radiation to the prostate and proximal seminal vesicles to 45 to 50.4 Gy in 25 to 28 fractions [56]. At 3 years, the freedom from biochemical recurrence was 100% for intermediate-risk and 89.8% for high-risk patients. A 2014 study retrospectively examined 97 patients (from all risk categories) treated with SBRT alone to a dose of 35 to 36.25 Gy in 5 fractions, or pelvic radiation to 45 Gy followed by an SBRT boost of 19 to 21 Gy in 3 fractions [57]. With a median follow-up of 60 months, freedom from biochemical recurrence was 69%. In multivariate analysis, there was no statistically significant difference in outcomes for patients treated with either SBRT alone or pelvic radiation with SBRT boost. A total of 5% of patients experienced Grade 2 to 3 GU toxicity and 7% of patients reported Grade 2 GI toxicity. Three additional studies (with fewer patients) reported similar outcomes with similar treatment schemes [58–60].

9. Conclusions

The use of radiation therapy for prostate cancer changed significantly over the past several decades. Concurrent with a deeper understanding of the biology of prostate cancer, medical technology has improved to a level where significantly higher doses of radiation can potentially be delivered with each fraction without compromising safety or efficacy. As discussed in this review, an impressive collection of literature supports the use of moderate hypofractionation or SBRT in appropriately selected patients. Indeed, recently released ASTRO guidelines now recommend moderate hypofractionation as a standard of care for low-, intermediate-, and high-risk men who opt to undergo definitive radiation treatment that does not include irradiation of pelvic lymph nodes. Moving forward, more work aimed at demonstrating the safety and efficacy of SBRT needs to be accomplished before its use gains widespread acceptance.

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