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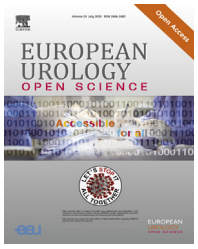

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Review – Prostate Cancer

Hypofractionated Postoperative Radiotherapy for Prostate Cancer: Is the Field Ready Yet?

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Abstract

Context: Radiotherapy (RT) is a valid adjuvant treatment for men with high-risk pathological features after radical prostatectomy and a salvage treatment for biochemical recurrence. A major inconvenience is that RT takes course over 7–8 wk in these settings, which has been shown to limit its use. Retrospective and pilot prospective investigations suggest that hypofractionation may provide noninferior outcomes but report variable results regarding toxicities. Additionally, our evolving understanding of prostate cancer radiobiology suggests that hypofractionated regimens may not increase toxicity.

Objective: We examine and review the rationale and clinical evidence of hypofractionated RT in the adjuvant and salvage settings for prostate cancer.

Evidence acquisition: We reviewed relevant literature, with a particular focus on recent studies employing hypofractionated RT.

Evidence synthesis: Hypofractionated RT in the adjuvant or salvage setting is not a standard option for prostate cancer RT outside of an investigational trial. While smaller studies show conflicting data regarding toxicity, initial evidence from larger clinical trials appears to demonstrate that hypofractionated postoperative RT is as effective and safe as conventionally fractionated courses.

Conclusions: With the growing acceptance of hypofractionation across other cancer sites and the rise of extreme hypofractionation for definitive prostate cancer treatment, hypofractionated postoperative therapy for prostate cancer is poised to become an option, as it may reduce the burden on men and treatment centers while maintaining clinical efficacy and safety. Prospective trials are currently ongoing to address efficacy and safety concerns.

Patient summary: Postoperative radiotherapy is a potentially curative treatment for patients with high-risk disease or recurrence after surgery. Shortening of the treatment regimen with the availability of modern treatment delivery techniques in conjunction with the integration of molecular imaging information to refine treatment volumes may improve therapeutic benefit without increasing toxicity.

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1. Introduction

Despite advances in detection and treatment of prostate cancer translating to improved overall survival, biochemical recurrence occurs in 20–40% of men [1]. A significant proportion of men with adverse features on surgical pathology or those with biochemical recurrence following prostatectomy undergo postoperative radiotherapy, referred to as adjuvant or salvage therapy, respectively. The relative radioresistance of prostate cancer resulted in the use of higher treatment doses to achieve improved biochemical control. With conventional fractionation regimens, dose escalation is performed by increasing the number of total treatments such that the course takes place over 7–8 wk. However, protracted regimens are inconvenient, leading to deferring of treatment despite the benefits [2]. Similar issues with definitive prostate treatment have been mitigated with the advent of several technological innovations in parallel with an improved understanding of radiobiology, allowing treatment time to be reduced from 8–9 wk to 4–6 wk or even 5 d. While hypofractionation is a standard for intact prostate cancer, its application is controversial and under investigation in the postoperative setting.

This review discusses the clinical indications for postoperative radiotherapy and the rationale for hypofractionation. We detail recent advances and updated results of clinical trials, which may allow for safe implementation of hypofractionated regimens. We explore future prospects and potential challenges to implement hypofractionation into routine clinical practice and discuss areas in which further clinical validation is necessary.

2. Evidence acquisition

We reviewed relevant literature, with a particular focus on recent studies employing hypofractionated radiotherapy.

3. Evidence synthesis

3.1. Overview of adjuvant and salvage radiotherapy

The risk of biochemical recurrence following prostatectomy is higher in men with a higher Gleason score, seminal vesicle invasion, extraprostatic extension, and positive surgical margins [3]. Three large trials, the German Cancer Society (ARO) 96-02, Southwest Oncology Group (SWOG) 8794, and the European Organization for Research and Treatment of Cancer (EORTC) 22911, established the role for adjuvant radiotherapy, reporting a 50% relative decrease in 10-yr biochemical recurrence, as well as improvements in local control and disease-free survival [4–6].

These trials reported biochemical-free survival rates of 40–54% at 5 yr for men who were observed after prostatectomy [4–6], suggesting that some men will not recur. Additionally, not all men with biochemical recurrence will develop clinical progression [7]. An area of active investigation is determining the subset of men who would derive the greatest benefit from postoperative radiotherapy. One method entails opting for salvage radiotherapy at the time of biochemical recurrence as an alternative to upfront adjuvant radiotherapy. This approach is supported by two recently reported trials, RAVES and Radiation and Androgen Deprivation In Combination after Local Surgery (RADICALS; NCT00860652 and NCT00541047, respectively).

3.2. Rationale for hypofractionation

The optimal dose and fractionation in the postoperative setting is not established. The ARO, SWOG, and EORTC trials used a conventional fractionation scheme with radiotherapy given over 6–7 wk at a dose of 60–64 Gy. Retrospective reports and smaller prospective studies have used higher doses, but without any discernable improvement [8], and are currently under investigation in the SAKK 09/10 trial (NCT01272050). Improvements in treatment delivery, greater understanding of prostate cancer radiobiology, and wider acceptance of regimens using higher doses over fewer treatments provide a rationale for hypofractionated postoperative radiotherapy.

The relative sensitivity of tissues to the size of the radiation dose and fractionation is reflected by the α/β ratio, with rapidly dividing tumors and acute responding tissues having higher ratios (10 Gy), and slow-growing tumors and late responding tissues having lower ratios ($\leq$3 Gy). Radiobiological analyses suggest that prostate cancer has a slow proliferation rate with an α:β ratio of 2:3 [9,10] or even as low as 1.5 [11], suggesting radiosensitivity similar to, or even lower than, that of adjacent organs at risk. Regardless of which α/β is most accurate, current biological dogma across several disease sites suggests that hypofractionated regimens will provide equivalent cancer control without increasing adverse effects. Additionally, biochemical control may improve with higher biological effective doses, supported by prospective phase 1 and 2 trials reporting improved biochemical recurrence–free survival using doses $\geq$70 Gy [12]. Thus, the inherent radioresistance of prostate cancer lends itself to achieve dose escalation through hypofractionation.

Several prospective randomized studies show comparable toxicity profiles and noninferior outcomes between conventional radiotherapy given over 9 wk and moderately hypofractionated regimens administered for 4–6 wk for intact prostate cancer [13,14]. Stereotactic body radiotherapy, an extremely hypofractionated regimen entailing five treatments of 7–10 Gy, is supported in National Comprehensive Cancer Network (NCCN) guidelines for definitive prostate treatment. Moderate and extreme hypofractionation are being increasingly employed for the definitive treatment of intact prostate cancer as physicians become more comfortable with the technique, outcomes, and side effect data [15].

The trend toward safe treatment of several sites with hypofractionated approaches is largely due to technological advances enabling dose-escalated treatment with high precision. Prostate radiotherapy has moved from two-dimensional techniques to using intensity-modulated radiotherapy (IMRT). The advent of IMRT allows for delivery of

highly conformal plans that selectively allow higher doses to areas of gross disease while sparing organs at risk. Additionally, the advent of image-guided radiotherapy allows positioning verification prior to or even during treatments, ensuring precise dose delivery. Thus, radiobiological and clinical data from intact prostate cancer provide a strong rationale for hypofractionation in the postoperative setting.

3.3. Challenges in delivery of hypofractionated radiotherapy

When radiotherapy is delivered in a hypofractionated manner, minimizing dose to neighboring organs is of paramount importance. Radiation dose constraints for organs at risk are based on the knowledge that irradiating a tissue volume beyond a given dose will increase the risk of adverse events. Compared with standardized computerized tomography (CT), integration of multiparametric magnetic resonance imaging with treatment planning has improved the definition of the target volume and organs at risk, such as the bladder, rectum, penile bulb, and neurovascular bundles [16]. There are important anatomical and dosimetric differences between definitive and postoperative radiotherapy that may give pause to implementing a hypofractionated approach. Following prostatectomy, a considerable amount of the bladder is displaced into the prostatic fossa along with the disruption of the fascial plane along the anterior rectal wall. Consequently, conventional postoperative radiotherapy plans encompass greater bladder volumes than intact prostate cancer, impairing the ability to meet tolerance dose constraints with hypofractionation. A better understanding of bladder tolerance to radiotherapy can aid in discerning appropriate dose limits. Another technique commonly employed to reduce irradiated bladder volume entails having men receiving each fraction with a full bladder. While effective, there can be issues with reproducibly filling the bladder to the same extent daily, limitations with incontinent men, and imposing patient discomfort.

3.4. Integrating molecular imaging

Target volumes for the prostatic fossa and regional nodal irradiation rely on conventional practice derived from anatomical knowledge, clinical experience, and established imaging, which can result in needlessly large treatment volumes [17]. Differences in defining the prostatic fossa and at-risk regional nodes influence clinical target volume concepts designed to cover microscopic tumor spread beyond that of the gross tumor volume. Major advances have been made in molecular imaging, which in contrast to anatomy-dependent imaging, such as CT and magnetic resonance imaging, depicts metabolic processes reflective of highly active tumor cells. Molecular imaging with 18F-fluorodeoxyglucose positron emission tomography (PET)/CT also has limited use in prostate cancer owing to its lower glucose uptake and slow growth [18]. Unlike bone scans, which detect any process inducing increased osteoblastic activity, newer modalities have the advantage of being specific to prostate cancer (Table 1).

3.4.1. Choline

Choline, a substrate for the synthesis of phosphatidylcholine, is upregulated in prostate carcinoma cells, promoting its use as a molecular marker to detect recurrence in the setting of biochemical failure [19]. A meta-analysis by Fanti et al [20] including 2686 patients from 29 studies showed that 11C-choline PET/CT was able to identify the site of relapse in 62% of cases. In a study of 115 patients with biochemical failure, 11C-choline PET/CT detected prostate bed recurrences with sensitivity and specificity, respectively, of 54% and 92%, compared with 88% and 84% with magnetic resonance imaging, but proved superior in detecting nodal metastases (92% vs 70%) [21]. The findings in these studies are reflective of 11C-choline's specificity affected by observations of increased uptake of both neoplastic and non-neoplastic cells, with the latter demonstrating higher avidity in some instances [22]. While there is no consensus on the optimal timing of 11C-choline scans for biochemical recurrence, the European Association of Urology recommends choline PET/CT for men with prostate-specific antigen (PSA) >1 ng/ml [23]. 11C-choline PET/CT is also approved by the Food and Drug Administration (FDA) as it provides better disease evaluation than fluorodeoxyglucose but remains suboptimal in light of the aforementioned and other studies. Notably, 11C-choline

Table 1 – PET tracers used in postoperative prostate cancer imaging

Tracer	Mechanism	Imaging indications	Strengths	Limitations	Relevant PSA range (ng/ml)
11C-choline	Higher uptake by prostate cancer cells during lipid membrane synthesis	Detection of disease recurrence in patients with rising PSA following surgery	Localizes cancer foci in lymph nodes, skeleton, and soft tissues	Suboptimal specificity	≥1
18F-fluciclovine	Higher uptake by prostate cancer cells due to higher amino acid requirements	Detection of disease recurrence in patients with rising PSA following surgery	Detects metastatic foci with higher rates than choline	Suboptimal specificity	≥1
68Ga-PSMA	Targets PSMA transmembrane receptor on prostate cells	Detection of disease recurrence in patients with rising PSA following surgery	Localizes cancer foci with high specificity and sensitivity Can detect recurrent lesions at lower PSA values	Pending approval in the USA	≥0.2

PET = positron emission tomography; PSA = prostate specific antigen; PSMA = prostate-specific membrane antigen.

radiotracers possess a 20-min half-life, necessitating an onsite cyclotron for clinical use. Given its practical and clinical limitations, 11C-choline's use in the setting of biochemical failure is declining in favor of newer biomarkers discussed below.

3.4.2. Fluciclovine

FDA has approved 18F-fluciclovine for use in the setting of biochemical recurrence on the basis of diagnostic findings, with histological confirmation demonstrating subject-level detection, positive predictive value, and specificity of 68%, 62%, and 70%, respectively [24]. Current NCCN guidelines recommend 18F-fluciclovine PET/CT for men with biochemical recurrence after primary treatment for following equivocal findings on bone and CT scans.

The 18F Fluciclovine PET/CT in Patients with Rising PSA after Initial Prostate Cancer Treatment (LOCATE) study recently reported the utility of 18F-fluciclovine imaging in men with biochemical failure following initial treatment. Of the 213 men with a median PSA of 1.00 ng/ml, 18F-fluciclovine–avid lesions were detected in 122. Overall, 18F-fluciclovine PET/CT led to drastic management changes for 126 men, of whom 32 originally recommended for salvage or noncurative systemic therapy were switched to watchful waiting, 30 were changed from noncurative systemic therapy to salvage therapy, and 11 were changed from salvage therapy to noncurative systemic therapy [25]. Thus, 18F-fluciclovine PET/CT may help select men who can safely be observed after prostatectomy despite high-risk features on pathology. In line with smaller studies [26], identification of 18F-fluciclovine–avid lesions can aid in defining radiotherapy target volumes. However, longer follow-up is warranted to determine the impact of these management changes on survival.

3.4.3. Prostate-specific membrane antigen

Among imaging modalities, 68Ga-labeled prostate-specific membrane antigen (PSMA) is able to detect prostate cancer with high specificity and sensitivity [27]. The largest study to date by Hoffman et al [28] evaluated the utility of 68Ga-PSMA PET/CT to detect disease in 660 men with biochemical failure following initial treatment. In 76% of men, 68Ga-PSMA PET/CT uptake was detected, which was associated with a Gleason score of $\geq$7, PSA velocity, and PSA level: men with PSA levels of 0.2–<0.5, 0.5–<1.0, 1.0–<2.0, 2.0–<5.0, and $\geq$5.0 ng/ml showed detection rates of 44.7%, 61.7%, 72.3%, 85.2%, and 94%, respectively. Thus, 68Ga-labeled PSMA has a high degree of sensitivity for detecting recurrent lesions even in men with low PSA values. This precision is underscored by the emergence of more sensitive PSA tests allowing earlier detection of biochemical recurrence. A recent prospectively paired study compared the ability of 18F-fluciclovine and PSMA PET-CT scans to localize recurrent prostate cancer following prostatectomy in men with biochemical recurrence with low PSA concentrations (<2.0 ng/ml). Among 50 men studied, overall detection rates were significantly superior with PSMA compared with 18F-fluciclovine (28 vs 13), as were detection of nodal metastases (15 vs four) and extrapelvic lesions (eight vs zero), promoting PSMA as the radioactive tracer of choice in detecting residual disease following biochemical failure [29]. A recent meta-analysis by Perera et al [30] including 37 studies comprising 4790 men evaluated the predictors of positive PSMA PET and attempted to identify patterns of detected PSMA-avid lesions. Positive detection rates at biochemical recurrence increased with higher PSA, but did not correlate with Gleason score $\leq$7 versus $\geq$8. More recurrences were detected in the prostate bed following radiotherapy (58%) versus prostatectomy (22%). However, patterns of nodal and distant metastases did not differ with primary treatment modality. The authors note that PSMA PET improves detection of metastases in biochemical recurrence with PSA levels as low as 0.2 ng/ml. While the European Association of Urology guidelines recommend PSMA PET-CT, routine use in the USA is pending FDA approval.

Clinically validated modern molecular imaging using highly specific tracers may enable earlier detection of residual and recurrent gross tumor volume both at the prostatic fossa and at regional lymphatics. Men initially presenting with biochemical failure may be salvaged successfully through improved methods to localize residual disease at an early time point. A major source of concern for physicians is whether to include lymph nodes in addition to the prostatic fossa. Prostate cancer–specific tracers can assist in accurately defining the extent of residual or recurrent disease, thus guiding the aggressiveness of postoperative therapy against the potential side effects of larger irradiation volumes. An additional corollary of these highly specific and sensitive scans is redefining target volumes, as the ability to localize microscopic disease may obviate the need to prophylactically cover clinical volumes that are traditionally at risk but potentially uninvolved. Adaptation of target volumes in line with these concepts may enable treatment escalation while reducing irradiation of normal tissues, thus addressing a major limitation for hypofractionating effectively and safely in the postoperative setting. Further study is needed to determine the relative merits of and indications for PSMA and fluciclovine. Additionally, long-term follow-up is necessary to determine whether there is a causal relationship of management changes using adjunct imaging modalities for diagnostics and treatment with improved outcomes.

3.5. Clinical evidence to date

As randomized trials are ongoing, there is currently no prospective phase III evidence comparing hypofractionated with conventionally fractionated postoperative prostate radiotherapy. Thus, current efficacy is largely based on retrospective analyses (Table 2). Lee et al [17] retrospectively evaluated men who underwent salvage radiotherapy for biochemical relapse following prostatectomy. The median PSA at the time of radiotherapy was 2.9 ng/ml (range: 0.5–11.4 ng/ml). A PSA response was seen in 33 (89%) [30]. In a similar study, Wong and colleagues [31] demonstrated with a median follow-up of 18.9 mo that 39 men had a biochemical response to salvage radiotherapy,

Table 2 – Studies reporting efficacy of hypofractionated radiotherapy for postoperative prostate cancer

Study	Patients (*n*)	Total dose (Gy)	Number of fractions	Technique	Median follow-up (mo)	Biochemical recurrence–free survival (%)	DM (%)	OS (%)	Acute gastrointestinal toxicity (≥G3), *n*	Acute genitourinary toxicity (≥G3), *n*	Late gastrointestinal toxicity (≥G3), *n*	Late genitourinary toxicity (≥G3), *n*
Lee et al (2018) [17]	61	50–52.5	20	3D	36	74	0	100	0	0	0	1
Wong et al,(2008) [31]	50	65–70	26–28	IMRT	24	72.9	2	96	0	0	0	0
Kruser et al (2011) [32]	108	65	26	IMRT	32.4	67	2.7	99	0	1	0	0
Lewis et al (2016) [33]	56	57.5–65	23–26	IMRT	48	75	NR	96	0	0	2	4
Fersino et al (2017) [34]	125	65.5–71.4	28–30	IMRT	18	85.5	NR	NR	0	1	0	2
Macchia et al (2017) [35]	124	62.5	25	IMRT	60	86.5	1	100	0	1	NR	NR
Tandberg et al (2018) [36]	167	65	26	IMRT	38.6	78.4	4	94.3	0	1	11	1
Picardi et al (2018) [37] [a]	918	50–72.8	20–29	2D, 3D and IMRT	36	74–85	NR	NR	NR	NR	NR	NR
Siepe et al (2018) [38] [a]	1208	37.8–74.2	21–28	3D and IMRT	60	86.5	NR	NR	0	NR	NR	NR
Chin et al (2020) [39]	112	52.5	20	3D	120	51.5	16	75	NR	NR	NR	NR

2D = two-dimensional volume imaging; 3D = three-dimensional conformal radiotherapy; G3 = grade 3; DM = distant metastases; IMRT = intensity-modulated radiation therapy; *n* = number of patients; NR = not reported; OS = overall survival.
[a] Systematic review.

three had an initial response followed by subsequent failure, and seven progressed. Lower PSA at the time of radiotherapy was the only factor prognostic of improved biochemical control. The cohort reported by Kruser et al [32] had a median presalvage PSA level of 0.44 ng/ml, and 17% received androgen deprivation therapy following prostatectomy or with radiotherapy. On multivariate analysis, higher Gleason scores and negative margins were associated with biochemical failure.

From a prospectively maintained database, Lewis et al [33] reported outcomes after adjuvant and salvage post-prostatectomy hypofractionated radiotherapy. Of the patients, 30% had preradiotherapy PSA < 0.1 ng/ml with a median PSA level of 0.32 ng/ml. Ten men were also treated with neoadjuvant and concurrent androgen deprivation therapy. This study was notable for a higher than anticipated rate of late grade 3 genitourinary toxicities, with all events resulting from gross hematuria approximately 2 yr after treatment. Purported explanations for this finding include longer follow-up periods and more precise daily imaging techniques inadvertently leading to more bladder coverage as the bladder falls within the prostatic fossa.

A few groups reported the outcomes with newer radiotherapy approaches. Fersino et al [34] evaluated acute toxicities from moderate hypofractionation delivered to the prostatic fossa with volumetric arc therapy. All 125 men completed the planned treatment successfully. A higher rate of grade ≥2 genitourinary side effects was found in the adjuvant setting than in the salvage group (17.1% vs 9.8%). Macchia et al [35] reported the outcomes of using hypofractionated radiotherapy delivered with a simultaneous integrated boost after prostatectomy, with biochemical control and acute and late toxicity rates comparable with traditional treatment schemes.

Recently, Tandberg and colleagues [36] compared outcomes in 294 men receiving conventional (66 Gy in 1.8–2 Gy fractions) with those in 167 men receiving hypofractionated radiotherapy (65 Gy in 2.5 Gy fractions) to the prostatic fossa. While 4-yr biochemical progression–free survival was 78% in the hypofractionated cohort and 65% in the conventional cohort, hypofractionation was not significant for biochemical progression–free survival on multivariate analysis. The hypofractionated cohort reported higher acute grade ≥2 genitourinary toxicity (22% vs 8%) and late ≥3 genitourinary toxicity at 6 yr (11% vs 4%), but was not associated with late grade ≥2 genitourinary toxicity on multivariate analysis. Notably, the hypofractionation cohort had significantly worse baseline urinary incontinence.

Picardi et al [37] performed a systematic review including 10 prospective and four retrospective studies. The majority of studies included men treated after the 2000s and followed the Radiation Therapy Oncology Group (RTOG) contouring guidelines to define the prostatic fossa. Biochemical failure rates ranged between 74% and 85% at 3 yr and between 67% and 75% at 4 yr. There was larger heterogeneity regarding late effects, which may be attributed to difference in follow-up and treatment technique. Another systematic review by Siepe et al [38] included

17 studies, of which seven were retrospective. Each of three-dimensional conformal radiotherapy and volumetric modulated arc therapy was used in two series, while 12 trials treated men with IMRT, of which five employed a simultaneous integrated boost. Seven studies treated only the prostatic fossa, and 10 targeted prostatic fossa and pelvic lymph nodes. There was more variation regarding the rates of late grade $\geq$2 gastrointestinal (range: 0–8.7%) and genitourinary (range: 0–66%) toxicities. The authors attributed the high late toxicity to outdated radiotherapy techniques in some of the included trials. They concluded that the use of androgen deprivation therapy and inclusion of regional lymph nodes did not worsen toxicity [38].

Chin et al [39] retrospectively evaluated 10-yr outcomes of treated men following prostatectomy for pT2-4N0M0 R0-1 prostate cancer between 2007 and 2009. Early salvage was defined as receiving radiotherapy with a PSA level of $\leq$2 ng/ml. They excluded men who received regional nodal irradiation. The cohort had a median PSA level of 0.4 ng/ml at the time of salvage radiotherapy and 14% received androgen deprivation therapy. Freedom from biochemical failure at 10 yr for early salvage versus late salvage was 68% versus 49%. Freedom from biochemical failure was associated with presalvage PSA, seminal vesicle invasion, and androgen deprivation therapy on multivariate analysis. Despite its retrospective nature, this study provides the longest follow-up of men treated with hypofractionated salvage radiotherapy and confirmed the findings of prior studies suggesting that salvage with PSA $\leq$ 0.2 confers improved cancer-specific, metastasis-free, and overall survival. Taken together, these findings suggest that hypofractionation is well tolerated for postoperative radiotherapy with early biochemical response rates consistent with those of conventional fractionation, but with conflicting data regarding toxicity.

The results of ongoing prospective randomized trials comparing conventionally fractionated postoperative prostate radiotherapy with moderately hypofractionated regimens will provide definitive comparisons of efficacy and adverse effects. The RADICALS phase III trial is comparing adjuvant versus early salvage radiotherapy along with the inclusion and duration of androgen deprivation therapy. The trial permitted a conventionally fractionated course of 66 Gy in 33 fractions or a moderately hypofractionated regimen of 52.5 Gy in 20 fractions [40]. Initial results showed no statistically significant difference in biochemical progression–free survival and freedom from subsequent hormonal therapy between adjuvant radiotherapy and early salvage radiotherapy at 5 yr in a cohort of 1396 men with intermediate- to high-risk localized prostate cancer who have undergone prostatectomy within 22 wk of enrollment, have a postoperative PSA level of $\leq$0.2 ng/ml, and have one or more of the following: (1) pT3/T4 disease, (2) Gleason 7–10 disease, (3) preoperative PSA $\geq$ 10 ng/ml, and (4) positive surgical margins. Of note, adjuvant radiotherapy was associated with an increased number of urinary and bowel adverse effects. The final results will provide comparative information of hypofractionation versus conventional fractionation. The ongoing NRG GU003 phase III randomized trial is prospectively comparing conventional post-prostatectomy radiotherapy using 66.6 Gy in 37 fractions with hypofractionation using 62.5 Gy in 25 fractions.

3.6. *Future perspectives*

Hypofractionated radiotherapy in the adjuvant or salvage settings is not a standard option for prostate cancer radiotherapy outside of an investigational trial. Prospective trials are currently ongoing to address efficacy and safety concerns. While smaller studies show conflicting data regarding toxicity, initial evidence from larger clinical trials appear to demonstrate that hypofractionated postoperative radiotherapy is equally effective and safe to conventionally fractionated courses. Essential information on this topic is currently being collected in the context of ongoing clinical trials, but these trials require long periods for follow-up and data maturation, affecting their impact at their time of publication. An optimistic endpoint to be determined from larger trials is whether the dose escalation afforded by hypofractionation translates into improved biochemical control. However, a more realistic outcome is showing that these approaches are noninferior to conventional fractionation with similar toxicity profiles.

4. Conclusions

In the current age of rapid technological innovation and personalized treatment approaches, early-phase trial data can be considered while awaiting data from randomized clinical trials. The ongoing phase III trials are essential to our understanding of the practicality, limitations, and efficacy of hypofractionated approaches to prevent biochemical recurrence in the adjuvant setting, or to address residual disease in the salvage setting. However, with the growing acceptance of hypofractionation across other cancer sites and the rise of extreme hypofractionation for definitive prostate cancer treatment, hypofractionated postoperative therapy for prostate cancer is poised to become an option, as it may reduce the burden on men and treatment centers while maintaining clinical efficacy. Additionally, men recommended for adjuvant or salvage treatment may be more likely to opt for shorter radiotherapy courses. More sensitive PSA testing, integration of highly specific radionucleotide tracers, more conformal treatment planning software, highly precise radiation delivery platforms, and the introduction of inter- and intrafraction image guidance may all add to the safety, efficacy, and attractiveness of hypofractionation.

Author contributions: Himanshu Nagar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Nagar, Mahase.
Acquisition of data: Nagar, Mahase.
Analysis and interpretation of data: Nagar, Mahase.
Drafting of the manuscript: Nagar, Mahase.

Critical revision of the manuscript for important intellectual content: Nagar, Mahase.
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