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Advances in radiotherapy for prostate cancer

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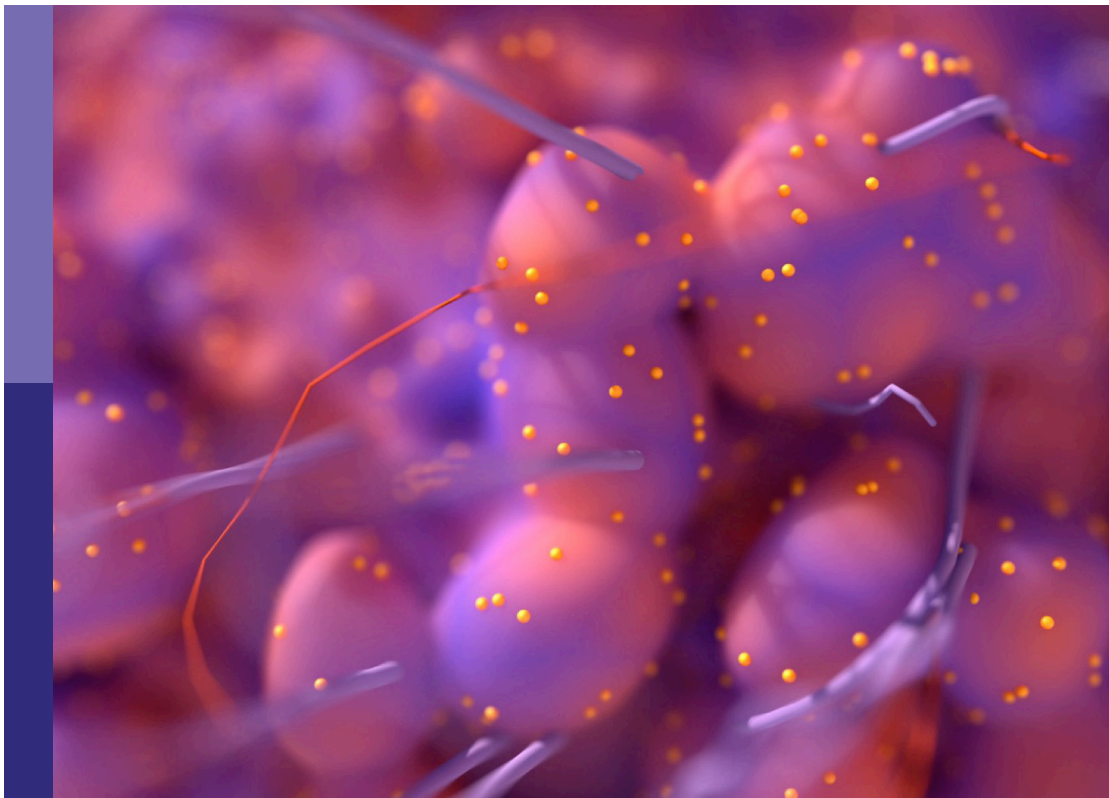
Published in
Frontiers in Oncology



ISSN 1664-8714
ISBN 978-2-83251-286-9
DOI 10.3389/978-2-83251-286-9

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Advances in radiotherapy for prostate cancer

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Citation

Zamboglou, C., Kamran, S. C., Kerkmeijer, L. G. W., eds. (2023). *Advances in radiotherapy for prostate cancer*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-83251-286-9

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frontiers | Frontiers in Oncology

TYPE Editorial
PUBLISHED 22 December 2022
DOI 10.3389/fonc.2022.1122652

OPEN ACCESS

EDITED AND REVIEWED BY
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SPECIALTY SECTION
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

RECEIVED 13 December 2022
ACCEPTED 14 December 2022
PUBLISHED 22 December 2022

CITATION
Kamran SC, Kerkmeijer LGW and Zamboglou C (2022) Editorial: Advances in radiotherapy for prostate cancer.
Front. Oncol. 12:1122652.
doi: 10.3389/fonc.2022.1122652

Editorial: Advances in radiotherapy for prostate cancer

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KEYWORDS

prostate cancer, radiation oncology, PSMA PET, stereotactic ablation body radiation therapy, oligometastasic prostate cancer, HDR brachytherapy, ARAT

Editorial on the Research Topic
Advances in radiotherapy for prostate cancer

Introduction

Prostate cancer (PCa) is the second most frequent cancer diagnosis in men worldwide and radiation therapy (RT) is a main treatment option for all disease stages. Recent developments in diagnostic medical imaging and high-precision RT techniques ensure that PCa patients can be cured while maintaining an excellent quality of life. In parallel, a deeper understanding of tumor biology facilitates the evolution from a "one size fits all approach" to a personalized therapy.

The goal of this Research Topic was to concentrate excellent and multidisciplinary scientific contributions on the evolving field of RT for PCa patients. The Research Topic accepted 13 articles including a total of 126 authors, demonstrating the rapid scientific progress in this field. The manuscripts of the Research Topic can be divided into the following topics according to the patient's disease stage.

Topic 1: Primary localized PCa

Definitive RT for patients with primary localized PCa is a main treatment option providing an excellent tumor control and maintaining the patient's quality of life. Current research for definitive RT for primary PCa patients includes the implementation of advanced imaging techniques for improved staging as well as focal dose escalation, the admission of new hormonal agents and the reduction of treatment time by delivering hypofractionated treatment regimen.

Two studies in the Research Topic evaluated the role of prostate specific membrane antigen positron emission tomography (PSMA-PET) for primary prostate cancer

patients. Zschaeck et al. examined retrospectively in 135 patients with PCa, which quantitative PSMA-PET parameters have the highest correlation with clinical and histological tumor aggressiveness. The authors concluded that SUVmax values in PSMA-PET show a superiority for the detection of high-risk patients with AUC values up to 0.73. Marinescu et al. performed an intraindividual comparison between [18F] PSMA-1007 PET/CT and multiparametric magnetic resonance imaging (mpMRI) in 93 primary PCa patients and reported a significant influence of PSMA-PET imaging on radiotherapy target volumes and the patients' cT stage; PSMA-PET detected significant more lesions and the PET-derived target volumes were significantly larger (2.05 *vs.* 3.65 ml, $p<0.01$). The authors concluded that combined mpMRI and PSMA-PET information should be used to guide focal dose escalation concepts.

Lara et al. presented the preliminary results of a prospective phase II study which assessed the effectiveness of 6 months enzalutamide monotherapy combined with hypofractionated external-beam radiotherapy (EBRT) for treating intermediate risk prostate cancer in 62 patients. The treatment was in general well tolerated with no significant changes in patients' quality of life. However, severe grade 3 acute systemic toxicity related to hypertension was observed in 19/56 (34%) patients. All the patients showed a prostate specific antigen (PSA) response 6 months after the end of Enzalutamide treatment. In a cost utility analysis by Farah et al. the authors compared robot-assisted Radical Prostatectomies (rRP) and robot-assisted stereotactic body radiotherapy in France. Stereotactic body radiotherapy seemed to be more cost-effective than rRP in terms of quality-adjusted life years (8.37 vs 6.85) despite the slightly higher initial cost due to the use of RT.

Finally, Tamihardja et al. evaluated the clinical outcome of two-weekly high-dose-rate brachytherapy boost after EBRT for 338 patients with localized prostate cancer. After a median follow-up of 101.8 months the authors observed an excellent toxicity profile with low GU/GI toxicity rates and effective long-term biochemical control (76% after ten years).

Topic 2: Elective nodal irradiation in patients submitted to radical, adjuvant or salvage RT

The role of elective nodal irradiation for intermediate/high/very-high risk non-metastatic prostate cancer is still debated. Thus, Guerini et al. present a preliminary analysis of the PRO-EP study, a multicenter observational study on Elective Pelvic nodes Irradiation (doi.org/10.3389/fonc.2022.951220). Forty-three centers enrolled 1029 patients. The follow-up, at this time, is too short to draw conclusions regarding cancer control outcomes, however, toxicity was mild, and there were no statistically significant differences in quality-of-life outcomes.

Topic 3: (Oligo)metastasized prostate cancer

There has been a paradigm shift in the understanding of metastatic PCa, particularly in the setting of advanced molecular imaging. Historically, metastatic prostate cancer was treated with systemic therapy, however, in recent years, the emergence of the "oligometastatic" disease state has led to novel indications for RT. At this time, oligometastatic prostate cancer is defined clinically, and can be broadly bucketed into *de novo* oligometastatic disease, oligorecurrent disease, and oligoprogressive disease, as detailed by Yaney et al. in their mini-review. They also highlight the emerging data behind the benefit of RT in these three indications. The authors discuss the need for large, randomized trials to further clarify which patients will benefit from metastasis-directed therapy, alluding to ongoing studies currently underway.

The definition of oligoprogressive disease can be vexing, with little data on the significance of oligoprogression in patients with castrate-resistant disease on novel antiandrogen therapy (e.g. androgen receptor-targeted therapy, ARTT, such as enzalutamide or abiraterone). Patel et al. evaluated 102 patients with metastatic castrate-resistant PCa (mCRPC) on ARTT at a single institution, finding that thirty (29%) of patients presented with oligoprogression and 21 patients (21% of total) had lesions suitable for SBRT. Most lesions were in the bone (46%) or lymph nodes (33%). Median progression-free survival to oligoprogression versus polyprogression was 16.8 versus 11 months. Time to further progression after oligoprogression was 13.6 months among those who received SBRT, versus 5.7 months in those treated with continuation of ARTT alone.

Xu et al. evaluated the efficacy and safety of SBRT (using CyberKnife) for PCa oligometastases in China. Between May 2012 and February 2021, 75 patients with 108 oligometastases were treated. With a median follow-up time of 23.2 months, the complete response, partial response, stable disease, and progressive disease rates were 63.0%, 10.2%, 21.3%, and 5.6% respectively. Among those with metastatic castration-resistant PCa, the 2-year local control rates were 93.8%, while for the 60 metastatic hormone-sensitive prostate cancer patients, the 2-year local control rates were 96.7%. In 27 patients not on androgen deprivation therapy, 2-year freedom from ADT was 44.0%. This study determined that SBRT is safe and effective.

Due to advances in imaging, the utility of biology-guided radiotherapy (BgRT) is an attractive and novel therapeutic modality to guide radiation therapy based on functional imaging. This was explored by Gaudreault et al. using PSMA-PET. The team described nodal and distant metastatic distribution of lesions to determine the proportion of metastatic lesions suitable for BgRT. Using a single-institution patient subset from the ProPSMA trial, the team contoured gross

tumor volumes (GTV) on the CT component of PSMA PET/CT scans. Lesions were considered suitable for biology-guided radiotherapy if 1) normalized SUV was larger than an nSUV threshold and 2) adjacent non-tumor tissue was free of PSMA-PET uptake inside the outer shell expansion. A majority of lesions evaluated were determined to be suitable for BgRT using a 10-mm tracking zone. Some lesions did have adjuvant non-tumor uptake, due to proximity of the ureter or bladder, and thus may require exclusion from emission tracking during BgRT. However, this represents a very novel technique to deliver treatment based on biological features of disease and incorporating this into radiation delivery, thus representing a potential role for efficient therapy of metastatic disease.

In patients who present with *de novo* lymph node-positive PCa, external beam radiation therapy (EBRT) + ADT is recommended as the preferred treatment option. Yet, the incorporation of PSMA-PET impacts EBRT treatment fields. The study by Spohn et al. sought to understand characteristics associated with biochemical recurrence after definitive radiotherapy when using PSMA-PET in the staging of clinically node positive patients. Forty-eight patients staged by PSMA-PET were included. All patients received EBRT to the pelvis +/- boost to positive nodes. With a median follow-up of 24 months, it was found that more than 2 PET-positive pelvic lymph nodes are associated with unfavorable biochemical recurrence-free survival, and high SUVmax values are associated with unfavorable metastasis-free survival. The authors suggest that these may be relevant prognostic factors to identify patients with favorable outcomes.

One important aspect when using high doses to treat the prostate, particularly in the setting of metastatic disease, is to ensure accurate visualization and targeting of delivery. Li et al. describe a case using daily MR-guided adaptive radiation therapy to treat a 65-year-old gentleman with metastatic PCa to his prostate. The patient received 36 Gy over 6 weekly fractions. The target volume had a marked 49% reduction – which was accounted for in the online adaptive process. This case report demonstrated the promising value for using the MR-linac for adaptive RT.

Cheng et al. then go on to describe a study protocol combining tislelizumab and multisite RT for patients with mCRPC. All patients had at least 1 site suitable for RT and failed ADT, followed by one novel second-line endocrine therapy. Patients received tislelizumab monotherapy induction therapy for two cycles, followed by one cycle combined with RT, followed by tislelizumab maintenance. The goal of this therapy is to potentially demonstrate a promising strategy for synergistic enhancement of treatment efficacy.

Conclusion

As demonstrated by the vast amount of unique research articles as part of this topic, PCa research is rapidly advancing in all disease stages. Definitive RT has been established in the treatment of primary PCa. The role of RT in oligometastatic disease will be elucidated and continue to evolve in this disease space. The coming years will see advances in imaging, techniques, combination therapies, and improved personalization of therapies.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

frontiers in Oncology

ORIGINAL RESEARCH
published: 26 November 2021
doi: 10.3389/fonc.2021.764536

Two-Weekly High-Dose-Rate Brachytherapy Boost After External Beam Radiotherapy for Localized Prostate Cancer: Long-Term Outcome and Toxicity Analysis

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OPEN ACCESS

Edited by:
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University Medical Center Utrecht, Netherlands

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *25 August 2021*
Accepted: *12 November 2021*
Published: *26 November 2021*

Citation:
Tamihardja J, Lutyj P, Kraft J, Lisowski D, Weick S, Flentje M and Polat B (2021) Two-Weekly High-Dose-Rate Brachytherapy Boost After External Beam Radiotherapy for Localized Prostate Cancer: Long-Term Outcome and Toxicity Analysis. Front. Oncol. 11:764536. doi: 10.3389/fonc.2021.764536

Purpose: Evaluation of clinical outcome of two-weekly high-dose-rate brachytherapy boost after external beam radiotherapy (EBRT) for localized prostate cancer.

Methods: 338 patients with localized prostate cancer receiving definitive EBRT followed by a two-weekly high-dose-rate brachytherapy boost (HDR-BT boost) in the period of 2002 to 2019 were analyzed. EBRT, delivered in 46 Gy (D_{Mean}) in conventional fractionation, was followed by two fractions HDR-BT boost with 9 Gy ($D_{90\%}$) two and four weeks after EBRT. Androgen deprivation therapy (ADT) was added in 176 (52.1%) patients. Genitourinary (GU)/gastrointestinal (GI) toxicity was evaluated utilizing the Common Toxicity Criteria for Adverse Events (version 5.0) and biochemical failure was defined according to the Phoenix definition.

Results: Median follow-up was 101.8 months. 15 (4.4%)/115 (34.0%)/208 (61.5%) patients had low-/intermediate-/high-risk cancer according to the D`Amico risk classification. Estimated 5-year and 10-year biochemical relapse-free survival (bRFS) was 84.7% and 75.9% for all patients. The estimated 5-year bRFS was 93.3%, 93.4% and 79.5% for low-, intermediate- and high-risk disease, respectively. The estimated 10-year freedom from distant metastasis (FFM) and overall survival (OS) rates were 86.5% and 70.0%. Cumulative 5-year late GU toxicity and late GI toxicity grade ≥ 2 was observed in 19.3% and 5.0% of the patients, respectively. Cumulative 5-year late grade 3 GU/GI toxicity occurred in 3.6%/0.3%.

Conclusions: Two-weekly HDR-BT boost after EBRT for localized prostate cancer showed an excellent toxicity profile with low GU/GI toxicity rates and effective long-term biochemical control.

Keywords: prostate cancer, high-dose-rate (HDR) brachytherapy, radiotherapy, long-term outcome, toxicity, external beam radiotherapy (EBRT), biochemical relapse free survival

INTRODUCTION

Prostate cancer represents the most common cancer type among adult men (1). Curative radiotherapy in localized disease is well established. Due to a low α/β - ratio of prostate cancer and subsequent high sensitivity to dose fractionation, hypofractionated and dose-escalated therapy regimes show an improved therapeutic ratio in the treatment of prostate cancer (2–5). However, keeping the limits of normal tissue tolerance for organs at risk remains difficult in dose-escalated external beam radiation therapy (EBRT). In contrast, high-dose-rate brachytherapy (HDR-BT) is able to deliver high single doses while respecting the dose constraints of the surrounding organs at risk. HDR-BT is also not quite as affected by the movement of organs at risk caused by organ filling compared to EBRT and offers excellent dose conformity. Nevertheless, there is concern that periprostatic disease, especially in high-risk cancer, is not treated sufficiently by HDR-BT alone. To obtain the advantages of both therapies, EBRT is often combined with a HDR-BT boost and randomized data has shown the superiority of the combination therapy over EBRT alone (6, 7).

Up to date, no standard treatment regime of combined EBRT and HDR-BT boost exists and the GEC/ESTRO guidelines state a wide range of possible regimes mostly based on published retrospective trials (8–20). While randomized trial data on this subject remains scarce, there is limited data on two-weekly HDR-BT boost after EBRT (**Figure 1**). This current publication reports long-term biochemical relapse-free survival and presents results of genitourinary and gastrointestinal toxicity in patients with localized prostate cancer treated with EBRT in combination with two-weekly high-dose-rate brachytherapy.

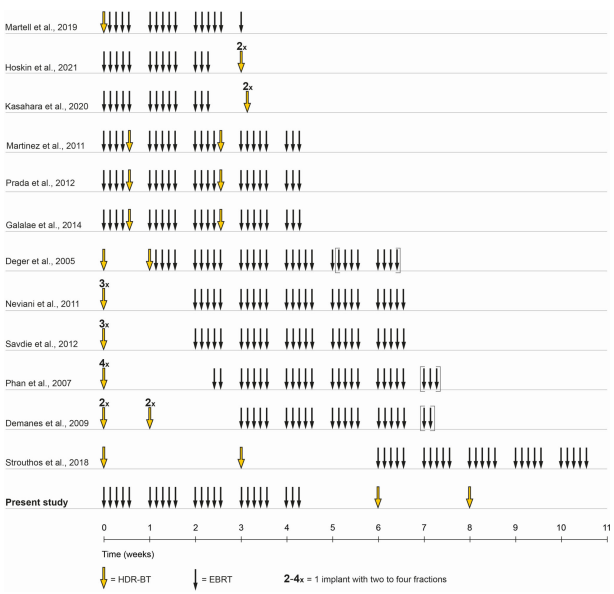

FIGURE 1 | Treatment schedule comparison. Shown is a comparison of timelines of combined EBRT and HDR-BT boost in the literature. In the present study, a treatment schedule with EBRT and two implants, two fractions HDR-BT boost was chosen. EBRT was administered in 4.5 weeks in 23 fractions of each 2 Gy. The first HDR-BT boost fraction with 9 Gy was applied one to two weeks after the end of EBRT with the second fraction following two weeks after.

MATERIALS AND METHODS

Patient Characteristics

This retrospective single-center analysis is based on 338 consecutive male patients treated between 2002 and 2019 with combined two-weekly high-dose-rate brachytherapy boost after external beam radiotherapy (EBRT) for localized prostate cancer. All patients had pathologically confirmed prostate cancer and were stratified into risk groups according to D'Amico et al. (21). During the implementation of the treatment protocol, a small number of low-risk patients were included. Later on, low-risk patients were excluded from dose-escalation by combined EBRT and HDR brachytherapy. Additive androgen deprivation therapy was recommended for patients with intermediate-risk (6 months) and high-risk disease (24–36 months) and prescribed at the discretion of the treating urologist. Staging examinations before radiotherapy included abdominal computed tomography, digital rectal examination, transrectal ultrasound (TRUS), prostate-specific antigen (PSA) serum testing, and bone scintigraphy. Magnetic resonance imaging (MRI) was not performed regularly as MRI assessment only became an internal standard during the study period. Biochemical failure was defined according to the Phoenix definition as nadir plus a ≥ 2 ng/ml increase in the prostate-specific antigen (PSA). Assessment of physician-recorded toxicity during radiotherapy was performed at baseline, at the end of the treatment, 6 weeks after treatment, and in 6 months intervals thereafter. After two years, follow-up was changed to longer periods with annual examinations. Gastrointestinal (GI) and genitourinary (GU) toxicity were scored using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Acute toxicity was defined as occurring within 3 months after radiotherapy. Late toxicity assessment included the 6 monthly and all later follow-ups.

External Beam Radiation Therapy

EBRT was delivered with 3D-conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), or volumetric-modulated arc therapy (VMAT) in 23 fractions with 2 Gy per fraction, resulting in a prescribed planning target volume (PTV) dose of 46 Gy (D_{Mean}). A clinical target volume (CTV) was generated consisting of the prostate and the seminal vesicles. The PTV was created by a 10 mm margin around the CTV in all but the dorsal direction, where a 7 mm margin was used. Pinnacle^3 (Philips Radiation Oncology Systems, Fitchburg, WI, USA) was used for treatment planning. Pelvic lymph node irradiation was performed depending on the individual decision and risk stratification.

HDR Brachytherapy Boost

Approximately two weeks after completion of EBRT, two HDR-BT boost fractions were performed with a 14-day interval between the two applications. Each session required new implantation. **Figure 1** illustrates the timing and sequence of

brachytherapy. Transperineal brachytherapy catheter implantation was performed with 3D TRUS-guided online planning in lithotomy position in general or spinal anesthesia by a small, limited group (n = 3) of brachytherapy experts. In 2008, the brachytherapy source was changed from Ir-192 to Co-60. As equipment for HDR-BT applications, the Multi-Source and SagiNova HDR afterloader (Eckert & Ziegler BEBIG GmbH) in combination with the treatment planning systems HDRplus, SagiPlan (Eckert & Ziegler BEBIG GmbH), and Nucletron PLATO were used. The HDR-BT boost PTV was defined as the entire prostate without the seminal vesicles and additional margin. The prescription dose for the PTV was 9 Gy ($D_{90\%}$) per fraction. The proportion of the PTV receiving 150% ($V_{150\%}$) should be below 50% and the $V_{200\%}$ below 25%. The maximum dose to the urethra was kept below 13 Gy (D_{Max}) and to the rectum below 9 Gy. An example of the 3D TRUS-supported intraoperative radiation planning is shown in **Figure 2**. The combined EBRT and HDR-BT boost resulted in a biologically effective dose (BED) of 233.33 Gy and an equivalent dose in 2 Gy fractions (EQD_2) of 100 Gy using an α/β-value of 1.5 Gy.

Statistics

Biochemical relapse-free survival, overall survival, prostate-specific survival, and freedom from distant metastasis were determined by the Kaplan–Meier method with associated log-rank testing for significant differences. Cox regression hazard model was applied for univariate and multivariate analyses adjusted to initial PSA, TNM stage, androgen deprivation therapy, and Gleason score. Differences were considered statistically significant in the case of a two-sided p-value of < 0.05. Statistical analysis was conducted using IBM SPSS v.26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The median follow-up of the whole cohort, consisting of 338 patients, was 101.8 (range 0.2–230.7) months. Classified by D'Amico, 15, 115, and 208 patients had low-, intermediate- and high-risk prostate cancer, respectively (21). Total treatment time was median 62 days (range 45-125 days) with a median time to first HDR-BT fraction of 14 days (range 2-76 days) after EBRT. Clinical characteristics are summarized in **Table 1**.

72 (21.3%) patients developed a biochemical relapse and in 37 (10.9%) patients distant metastases occurred during follow-up. The estimated biochemical relapse-free survival (bRFS), freedom from distant metastasis (FFM), and overall survival (OS) at 5 years were 84.7%, 93.4%, and 90.1%, respectively. At 10 years the estimated bRFS, FFM, and OS in our patient sample were 75.9%, 86.5%, and 70.0%, respectively. **Figure 3** shows the bRFS for each risk group according to the D`Amico classification.

Parameters for Cox regression analyses were TNM stage (≤T2b; ≥T2c), Gleason score ≤7a (3 + 4) *versus* ≥7b (4 + 3), initial PSA (continuous variable), ADT, Age (continuous variable), and MRI before treatment. Gleason score was found to be a prognostic factor for bRFS, FFM, and OS in both univariate and multivariate analyses. Initial PSA was a significant prognostic factor in multivariate analysis for bRFS, but not for FFM and OS. In multivariate analysis, TNM stage was prognostic for FFM, but not for bRFS and OS. ADT was not prognostic for bRFS, FFM, and OS in multivariate analysis in the whole patient cohort, in the intermediate-risk group, and the high-risk group. MRI was not prognostic for any outcome parameter. Age was a significant prognostic factor for OS. PSA kinetics were not available for analysis and, therefore, we cannot exclude them from being residual confounders. The results of the Cox regression analysis are summarized in **Table 2**.

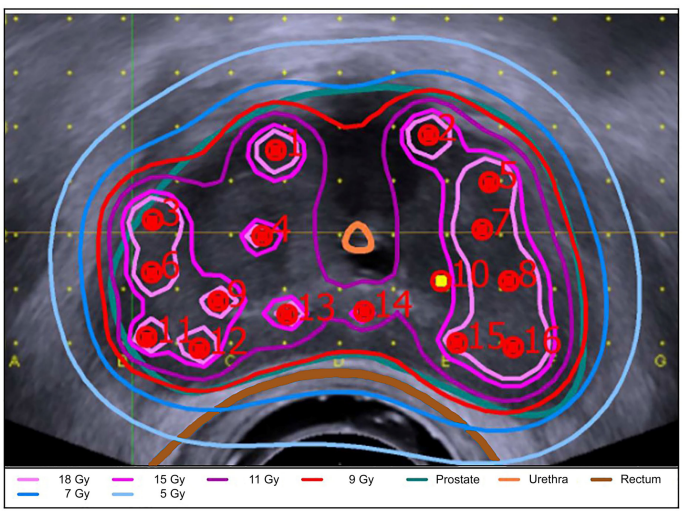

FIGURE 2 | 3D TRUS-supported intraoperative radiation planning. Shown is the 3D TRUS-supported intraoperative radiation planning using the SagiPlan treatment planning system (Eckert & Ziegler BEBIG GmbH). The prostate (turquoise), rectum (brown), intraprostatic urethra (orange) and the isodose distribution are shown in an axial view. The isodose distribution is coded with the following colours: light pink = 18 Gy ($D_{180\%}$); pink = 15 Gy ($D_{150\%}$); purple = 11.0 Gy ($D_{110\%}$); red = 9 Gy (D_{ref}); blue = 7 Gy ($D_{70\%}$); light blue= 5 Gy ($D_{50\%}$).

TABLE 1 | Patient and treatment characteristics.

Characteristics	(n=338)
Median age in years (range)	69.0 (50.0-81.3)
Median KPS in % (range)	90 (30-100)
Median iPSA in ng/mL (range)	10.1 (0.4-233.0)
iPSA group	
< 10 ng/mL	164 (48.5%)
10-20 ng/mL	88 (26.0%)
> 20 ng/mL	86 (25.4%)
N/A	0 (0%)
Gleason-Score	
≤ 6	63 (18.6%)
7a	102 (30.2%)
7b	71 (21.0%)
8 - 10	100 (29.6%)
N/A	2 (0.6%)
T-Stage	
T1	154 (45.6%)
T2	116 (34.3%)
T3	68 (20.1%)
T4	0 (0%)
N/A	0 (0%)
D`Amico risk group	
Low-risk	15 (4.4%)
Intermediate-risk	115 (34.0%)
High-risk	208 (61.5%)
N/A	0 (0%)
Lymph node irradiation	116/338 (34.3%)
Low-risk	4/15 (26.7%)
Intermediate-risk	17/115 (14.8%)
High-risk	95/208 (45.7%)
Androgen deprivation therapy	176/338 (52.1%)
Low-risk	6/15 (40%)
Intermediate-risk	36/115 (31.3%)
High-risk	134/208 (64.4%)
Imaging before treatment	
MRI	79 (23.4%)
PET-CT	19 (5.6%)
Treatment technique	
3D conformal	205 (60.7%)
IMRT	27 (8.0%)
VMAT	106 (31.4%)

KPS, Karnofsky Performance Status; N/A, not available; iPSA, initial prostate-specific antigen; 3D-CRT, 3D-conformal radiation therapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric-modulated arc therapy.

The temporal occurrence of GI and GU toxicity is shown in **Figure 4**. Late grade 2 GI toxicity peaked at the 12-month follow-up, decreased thereafter, and showed a second peak in the very late follow-up period after 60 months. No grade 4 GI toxicities were observed. One patient with rectal hemorrhage developed late grade 3 (0.3%) GI toxicity cumulated over 5 years of follow-up. Overall, a cumulative 5-year late GI toxicity grade ≥ 2 was observed in 5.0% of the patients. Late grade 2 to 3 GU toxicity showed a constant increase from the 24-month follow-up until the very late follow-up period after 60 months of follow-up. No grade 4 toxicities were observed. After 5 years of follow-up, 12 patients (3.6%) developed late grade 3 GU toxicity: All 12 patients suffered from late grade 3 urinary tract obstruction with 1 out of 12 developing additional grade 3 non-infective cystitis and urinary incontinence. Overall, a cumulative 5-year late GU toxicity grade ≥ 2 was observed in 19.3% of the patients.

DISCUSSION

Dose-escalation has demonstrated the ability to increase biochemical control in the management of prostate cancer. In this context, HDR-BT boost offers the possibility of highly conformal dose-escalation with excellent adjacent organ at risk sparing and has compared favorably to EBRT alone in the literature (6, 22–24). Our analysis differs from other published data by the applied treatment schedule: HDR brachytherapy was applied sequentially two and four weeks after EBRT, resulting in a total treatment time of median 62 days (**Figure 1**). A strength of the presented study is the absence of changes in the target volume definition or fractionation scheme, as all patients were treated with a standardized protocol. The matured median follow-up of 101.8 months, therefore, allows a comparison to updated randomized long-term data on HDR-BT boost: Hoskin et al. investigated hypofractionated EBRT alone or in combination with HDR-BT boost: treatment was randomized to 55 Gy in 20 fractions or 35.75 Gy in 13 fractions with 17 Gy HDRBRT boost in two fractions. A statistically significant difference in biochemical failure-free survival was demonstrated in favor of the combined modality and remained significant in the 12-year data update. GU and GI toxicity was not significantly different between both treatment arms (6). Sathya et al. randomized combined 35 Gy low-dose-rate (LDR) brachytherapy with EBRT of 40 Gy in 20 fractions *versus* EBRT of 66 Gy in 33 fractions. Biochemical control was improved for the combined treatment arm but failed to reach statistical significance in a recent update (22, 23). Looking beyond HDR-BT boost, the ASCENDE-RT trial compared dose-escalated EBRT of 78 Gy to EBRT of 46 Gy combined with 115 Gy LDR brachytherapy boost (25). 7-year biochemical failure-free survival in the LDRBT boost arm was 86% and 75% in the EBRT arm and therefore significantly increased for the combination therapy. Late GU toxicity was increased with 5-year grade 3 GU toxicity of 18.4% for LDRBT boost and 5.2% for the EBRT-only arm ($p < 0.001$). Recently, the phase 2 RTOG 0321 trial reported the results of 45 Gy EBRT in 25 fractions in combination with 19 Gy HDR-BT boost in two fractions within 24 hours: Biochemical failure rates per Phoenix definition at 5 and 10 years were 14% and 23% and the cumulative grade 3-5 GU/GI toxicity was 4% at 5 years (26).

Our outcome data is comparable to large retrospective analyses and randomized trials with a reported estimated 5-year bRFS, FFM, and OS of 84.7%, 93.4%, 90.1%, respectively for all patients and estimated 5-year bRFS of 79.5% for high-risk patients. Cumulative 5-year late grade 3 GU/GI toxicity occurred in 3.6/0.3% of the patients and is within the range of reported late toxicity incidence of randomized HDR-BT boost trials (6, 23, 26). In the present study, no evidence of compromised biochemical control by two-weekly HDR-BT boost after EBRT and the resulting long treatment time could be detected compared to the literature (**Supplementary Table 1**). The assumed proliferation equivalent of 0.24 Gy per day for EBRT alone might play a subordinate role when ultra-high single doses are used, as in HDR brachytherapy or stereotactic body radiotherapy (27, 28).

Currently, there is a general trend to shorter treatment courses by reducing the number of HDR brachytherapy fractions. We

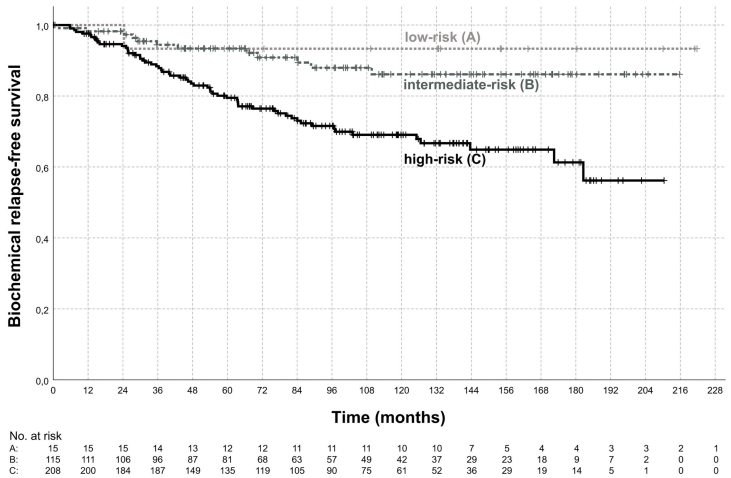

FIGURE 3 | Biochemical relapse-free survival. Shown is the biochemical relapse-free survival according to risk group for the low-risk group **(A)**, intermediate-risk group **(B)**, and high-risk group **(C)**. The estimated biochemical relapse-free survival at 5-years was 93.3%, 93.4%, 79.5% for low-, intermediate-, high-risk disease, respectively. Biochemical relapse-free survival was significantly different between intermediate-risk and high-risk ($p < 0.01$, log-rank test).

TABLE 2 | Cox regression analysis.

Variable		BRFS (N = 332; N/A = 6)			FFM (N = 331; N/A = 7)			OS (N = 334; N/A = 4)		
	N	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
TNM										
<T2C	222	1.00						1.00		
≥T2C	116	1.56	0.96-2.53	0.07	2.07	1.03-4.17	0.04	1.05	0.72-1.52	0.82
GLS										
<7b	165	1.00						1.00		
≥7b	171	3.03	1.77-5.18	< 0.01	5.29	2.24-12.52	< 0.01	1.75	1.19-2.57	< 0.01
iPSA (cv)	338	1.01	1.00-1.01	0.01	1.00	0.99-1.01	0.51	1.00	1.00-1.01	0.64
ADT										
No	162	1.00						1.00		
Yes	176	0.84	0.50-1.41	0.51	0.95	0.46-1.99	0.90	1.11	0.76-1.63	0.60
MRI										
No	259	1.00						1.00		
Yes	79	0.88	0.47-1.66	0.70	0.57	0.20-1.61	0.29	0.70	0.35-1.41	0.32
Age (cv)	338	0.99	0.96-1.03	0.73	0.97	0.93-1.02	0.30	1.04	1.01-1.07	0.02

bRFS, biochemical relapse-free survival; FFM, freedom from distant metastasis; OS, overall survival; iPSA, initial prostate-specific antigen; N/A, not available; HR, hazard ratio; CI, convidence interval; CV, continuous variable.

chose to implement two fraction HDR-BT boost in two separate sessions to improve patient compliance and to reduce the risk of catheter displacement compared to two brachytherapy fractions within 24 hours. Furthermore, in the monotherapy setting, single fraction HDR brachytherapy was recently shown to be inferior to two fraction HDR brachytherapy by Morton et al. (29).

The role of additional ADT in prostate brachytherapy remains debatable as the literature shows heterogeneity. A recent network meta-analysis of randomized trials by Jackson et al. showed an 88% probability that EBRT combined with ADT leads to an improved OS compared to EBRT combined with brachytherapy in intermediate- and high-risk disease (30). On the other hand, a systematic literature overview of the American Brachytherapy Society Task Group, including 52 studies with 43303 patients, showed no benefit for the addition of ADT to brachytherapy in low-risk and favorable intermediate-risk patients as well as most HDR brachytherapy trials (31). Keyes et al. observed an improvement in biochemical progression-free survival of up to 15% for the addition of ADT to brachytherapy for unfavorable intermediate- and high-risk patients as well as patients with suboptimal dosimetry at the cost of a potential overall survival detriment (31). Consistent with a large number of retrospective studies, our data did not demonstrate a benefit of additional ADT in bRFS, FFM, and OS in multivariate Cox regression analysis for the whole patient cohort, the intermediate-risk group as well as the high-risk group.

The findings from our retrospective study require further investigation in randomized controlled trials. Nevertheless, our analysis demonstrated promising biochemical control and low toxicity rates for two-weekly HDR-BT boost after EBRT.

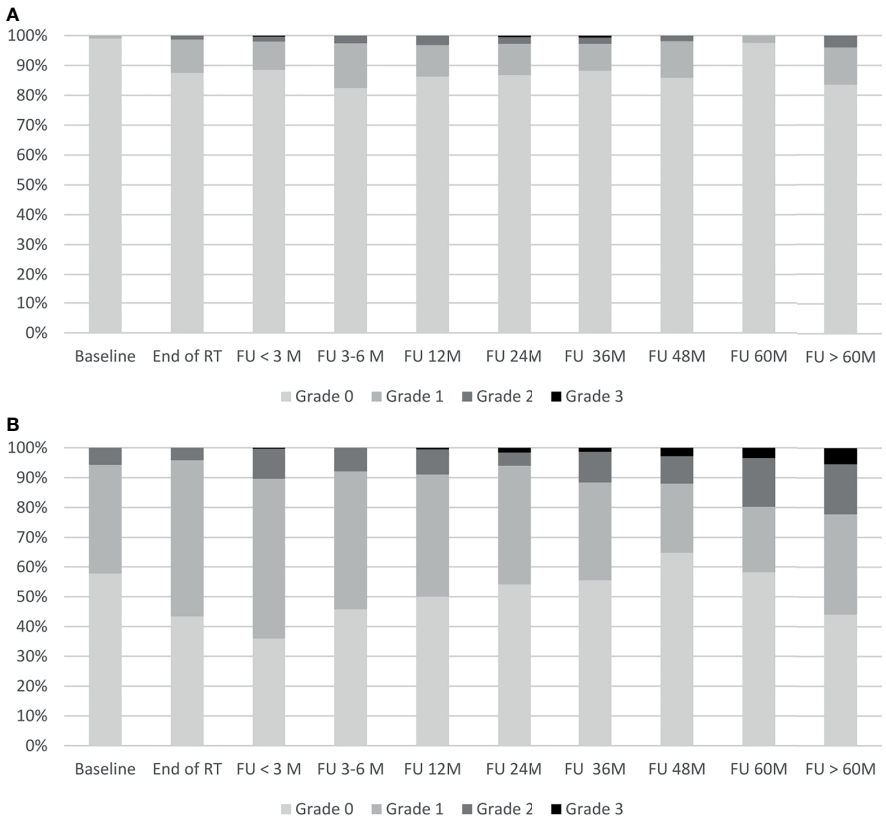

FIGURE 4 | Gastrointestinal and genitourinary toxicity. Shown is the time course of physician-recorded gastrointestinal toxicity **(A)** and genitourinary toxicity **(B)** according to CTCAE v5.0. RT, radiotherapy; M, months; FU, follow-up.

CONCLUSIONS

Two-weekly HDR brachytherapy boost after EBRT for localized prostate cancer is safe and feasible. With excellent biochemical control and low rates of gastrointestinal and genitourinary toxicities, two-weekly HDR brachytherapy boost can be considered as a standard treatment regime in clinical practice. The addition of ADT to combined HDR-BT boost and EBRT did not improve clinical outcome.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and written informed consent was not required for participation in this retrospective analysis in accordance with the local legislation [BayKrG Art. 27 (4)] and institutional requirements. Written informed consent for treatment and retrospective data analysis was provided by all patients before start of treatment.

AUTHOR CONTRIBUTIONS

JT, MF, and BP contributed to conception and design of the study. JT, PL, DL, and SW organized the database. JT performed the statistical analysis. JT wrote the first draft of the manuscript. PL and JK performed critical revision of the article for important intellectual content. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

This publication was supported by the Open Access Publication Fund of the University of Wuerzburg.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.764536/full#supplementary-material

REFERENCES

1. Barsouk A, Padala SA, Vakiti A, Mohammed A, Saginala K, Thandra KC, et al. Epidemiology, Staging and Management of Prostate Cancer. *Med Sci (Basel)* (2020) 8(3):28. doi: 10.3390/medsci8030028
2. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, et al. Conventional *Versus* Hypofractionated High-Dose Intensity-Modulated Radiotherapy for Prostate Cancer: 5-Year Outcomes of the Randomised, non-Inferiority, Phase 3 CHHiP Trial. *Lancet Oncol* (2016) 17(8):1047–60. doi: 10.1016/S1470-2045(16)30102-4
3. de Vries KC, Wortel RC, Oomen-de Hoop E, Heemsbergen WD, Pos FJ, Incrocci L. Hyprofractionated *Versus* Conventionally Fractionated Radiation Therapy for Patients With Intermediate- or High-Risk, Localized, Prostate Cancer: 7-Year Outcomes From the Randomized, Multicenter, Open-Label, Phase 3 HYPRO Trial. *Int J Radiat Oncol Biol Phys* (2020) 106(1):108–15. doi: 10.1016/j.ijrobp.2019.09.007
4. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-Hypofractionated *Versus* Conventionally Fractionated Radiotherapy for Prostate Cancer: 5-Year Outcomes of the HYPO-RT-PC Randomised, non-Inferiority, Phase 3 Trial. *Lancet* (2019) 394(10196):385–95. doi: 10.1016/S0140-6736(19)31131-6
5. Kerkmeijer LGW, Groen VH, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. *J Clin Oncol* (2021) 39(7):787–96. doi: 10.1200/JCO.20.02873
6. Hoskin PJ, Rojas AM, Ostler PJ, Bryant L, Lowe GJ. Randomised Trial of External-Beam Radiotherapy Alone or With High-Dose-Rate Brachytherapy for Prostate Cancer: Mature 12-Year Results. *Radiother Oncol* (2021) 154:214–9. doi: 10.1016/j.radonc.2020.09.047
7. Hoskin PJ, Motohashi K, Bownes P, Bryant L, Ostler P. High Dose Rate Brachytherapy in Combination With External Beam Radiotherapy in the Radical Treatment of Prostate Cancer: Initial Results of a Randomised Phase Three Trial. *Radiother Oncol* (2007) 84(2):114–20. doi: 10.1016/j.radonc.2007.04.011
8. Hoskin PJ, Colombo A, Henry A, Niehoff P, Paulsen Hellebust T, Siebert FA, et al. GEC/ESTRO Recommendations on High Dose Rate Afterloading Brachytherapy for Localised Prostate Cancer: An Update. *Radiother Oncol* (2013) 107(3):325–32. doi: 10.1016/j.radonc.2013.05.002
9. Demanes DJ, Rodriguez RR, Schour L, Brandt D, Altieri G. High-Dose-Rate Intensity-Modulated Brachytherapy With External Beam Radiotherapy for Prostate Cancer: California Endocurietherapy's 10-Year Results. *Int J Radiat Oncol Biol Phys* (2005) 61(5):1306–16. doi: 10.1016/j.ijrobp.2004.08.014
10. Demanes DJ, Brandt D, Schour L, Hill DR. Excellent Results From High Dose Rate Brachytherapy and External Beam for Prostate Cancer are Not Improved by Androgen Deprivation. *Am J Clin Oncol* (2009) 32(4):342–7. doi: 10.1097/COC.0b013e31818cd277
11. Deger S, Boehmer D, Roigas J, Schink T, Wernecke KD, Wiegel T, et al. High Dose Rate (HDR) Brachytherapy With Conformal Radiation Therapy for Localized Prostate Cancer. *Eur Urol* (2005) 47(4):441–8. doi: 10.1016/j.eururo.2004.11.014
12. Neviani CB, Miziara MA, de Andrade Carvalho H. Results of High Dose-Rate Brachytherapy Boost Before 2D or 3D External Beam Irradiation for Prostate Cancer. *Radiother Oncol* (2011) 98(2):169–74. doi: 10.1016/j.radonc.2011.01.005
13. Prada PJ, Mendez L, Fernandez J, Gonzalez H, Jimenez I, Arrojo E. Long-Term Biochemical Results After High-Dose-Rate Intensity Modulated Brachytherapy With External Beam Radiotherapy for High Risk Prostate Cancer. *Radiat Oncol* (2012) 7:31. doi: 10.1186/1748-717X-7-31
14. Savdie R, Symons J, Spernat D, Yuen C, Pe Benito RA, Haynes AM, et al. High-Dose Rate Brachytherapy Compared With Open Radical Prostatectomy for the Treatment of High-Risk Prostate Cancer: 10 Year Biochemical Freedom From Relapse. *BJU Int* (2012) 110 Suppl 4:71–6. doi: 10.1111/j.1464-410X.2012.11480.x
15. Phan TP, Syed AM, Puthawala A, Sharma A, Khan F. High Dose Rate Brachytherapy as a Boost for the Treatment of Localized Prostate Cancer. *J Urol* (2007) 177(1):123–7; discussion 7. doi: 10.1016/j.juro.2006.08.109
16. Martell K, Mendez LC, Chung HT, Tseng CL, Alayed Y, Cheung P, et al. Results of 15Gy HDR-BT Boost Plus EBRT in Intermediate-Risk Prostate Cancer: Analysis of Over 500 Patients. *Radiother Oncol* (2019) 141:149–55. doi: 10.1016/j.radonc.2019.08.017
17. Galalae RM, Zakikhany NH, Geiger F, Siebert FA, Bockelmann G, Schultze J, et al. The 15-Year Outcomes of High-Dose-Rate Brachytherapy for Radical Dose Escalation in Patients With Prostate Cancer - a Benchmark for High-Tech External Beam Radiotherapy Alone? *Brachytherapy* (2014) 13(2):117–22. doi: 10.1016/j.brachy.2013.11.002
18. Strouthos I, Chatzikonstantinou G, Zamboglou N, Milickovic N, Papaioannou S, Bon D, et al. Combined High Dose Rate Brachytherapy and External Beam Radiotherapy for Clinically Localised Prostate Cancer. *Radiother Oncol* (2018) 128(2):301–7. doi: 10.1016/j.radonc.2018.04.031
19. Kasahara T, Ishizaki F, Kazama A, Yuki E, Yamana K, Maruyama R, et al. High-Dose-Rate Brachytherapy and Hypofractionated External Beam Radiotherapy Combined With Long-Term Androgen Deprivation Therapy for Very High-Risk Prostate Cancer. *Int J Urol* (2020) 27(9):800–6. doi: 10.1111/iju.14305
20. Vigneault E, Mbodji K, Magnan S, Despres P, Lavallee MC, Aubin S, et al. High-Dose-Rate Brachytherapy Boost for Prostate Cancer Treatment: Different Combinations of Hypofractionated Regimens and Clinical Outcomes. *Radiother Oncol* (2017) 124(1):49–55. doi: 10.1016/j.radonc.2017.06.012
21. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer. *JAMA* (1998) 280(11):969–74. doi: 10.1001/jama.280.11.969
22. Sathya JR, Davis IR, Julian JA, Guo Q, Daya D, Dayes IS, et al. Randomized Trial Comparing Iridium Implant Plus External-Beam Radiation Therapy With External-Beam Radiation Therapy Alone in Node-Negative Locally Advanced Cancer of the Prostate. *J Clin Oncol* (2005) 23(6):1192–9. doi: 10.1200/JCO.2005.06.154
23. Dayes IS, Parpia S, Gilbert J, Julian JA, Davis IR, Levine MN, et al. Long-Term Results of a Randomized Trial Comparing Iridium Implant Plus External Beam Radiation Therapy With External Beam Radiation Therapy Alone in Node-Negative Locally Advanced Cancer of the Prostate. *Int J Radiat Oncol Biol Phys* (2017) 99(1):90–3. doi: 10.1016/j.ijrobp.2017.05.013
24. Kishan AU, Cook RR, Ciezki JP, Ross AE, Pomerantz MM, Nguyen PL, et al. Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer. *JAMA* (2018) 319(9):896–905. doi: 10.1001/jama.2018.0587
25. Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, et al. Androgen Suppression Combined With Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys* (2017) 98(2):275–85. doi: 10.1016/j.ijrobp.2016.11.026
26. Hsu IC, Rodgers JP, Shinohara K, Purdy J, Michalski J, Roach M3rd, et al. Long-Term Results of NRG Oncology/RTOG 0321: A Phase II Trial of Combined High Dose Rate Brachytherapy and External Beam Radiation Therapy for Adenocarcinoma of the Prostate. *Int J Radiat Oncol Biol Phys* (2021) 110(3):700–7. doi: 10.1016/j.ijrobp.2020.11.008
27. Alayed Y, Quon H, Ong A, Cheung P, Chu W, Chung H, et al. Accelerating Prostate Stereotactic Ablative Body Radiotherapy: Efficacy and Toxicity of a Randomized Phase II Study of 11 *Versus* 29 Days Overall Treatment Time (PATRIOT). *Radiother Oncol* (2020) 149:8–13. doi: 10.1016/j.radonc.2020.04.039
28. Thames HD, Kuban D, Levy LB, Horwitz EM, Kupelian P, Martinez A, et al. The Role of Overall Treatment Time in the Outcome of Radiotherapy of Prostate Cancer: An Analysis of Biochemical Failure in 4839 Men Treated Between 1987 and 1995. *Radiother Oncol* (2010) 96(1):6–12. doi: 10.1016/j.radonc.2010.03.020
29. Morton G, McGuffin M, Chung HT, Tseng CL, Helou J, Ravi A, et al. Prostate High Dose-Rate Brachytherapy as Monotherapy for Low and Intermediate Risk Prostate Cancer: Efficacy Results From a Randomized Phase II Clinical Trial of One Fraction of 19 Gy or Two Fractions of 13. *5 Gy Radiother Oncol* (2020) 146:90–6. doi: 10.1016/j.radonc.2020.02.009
30. Jackson WC, Hartman HE, Dess RT, Birer SR, Soni PD, Hearn JWD, et al. Addition of Androgen-Deprivation Therapy or Brachytherapy Boost to External Beam Radiotherapy for Localized Prostate Cancer: A Network Meta-Analysis of Randomized Trials. *J Clin Oncol* (2020) 38(26):3024–31. doi: 10.1200/JCO.19.03217

31. Keyes M, Merrick G, Frank SJ, Grimm P, Zelefsky MJ. American Brachytherapy Society Task Group Report: Use of Androgen Deprivation Therapy With Prostate Brachytherapy-A Systematic Literature Review. *Brachytherapy* (2017) 16(2):245–65. doi: 10.1016/j.brachy.2016.11.017

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frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 12 April 2022
doi: 10.3389/fonc.2022.854589

Utility of Biology-Guided Radiotherapy to *De Novo* Metastases Diagnosed During Staging of High-Risk Biopsy-Proven Prostate Cancer

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: 14 January 2022
Accepted: 23 February 2022
Published: 12 April 2022

Citation:
Gaudreault M, Chang D, Hardcastle N, Jackson P, Kron T, Hanna GG, Hofman MS and Siva S (2022) Utility of Biology-Guided Radiotherapy to De Novo Metastases Diagnosed During Staging of High-Risk Biopsy-Proven Prostate Cancer. Front. Oncol. 12:854589. doi: 10.3389/fonc.2022.854589

Background: Biology-guided radiotherapy (BgRT) uses real-time functional imaging to guide radiation therapy treatment. Positron emission tomography (PET) tracers targeting prostate-specific membrane antigen (PSMA) are superior for prostate cancer detection than conventional imaging. This study aims at describing nodal and distant metastasis distribution from prostate cancer and at determining the proportion of metastatic lesions suitable for BgRT.

Methods: A single-institution patient subset from the ProPSMA trial (ID ACTRN12617000005358) was analysed. Gross tumour volumes (GTV) were delineated on the CT component of a PSMA PET/CT scan. To determine the suitability of BgRT tracking zones, the normalized SUV (nSUV) was calculated as the ratio of SUVmax inside the GTV to the SUVmean of adjacent three-dimensional shells of thickness 5 mm/10 mm/20 mm as a measure of signal to background contrast. Targets were suitable for BgRT if (1) nSUV was larger than an nSUV threshold and (2) non-tumour tissue inside adjacent shell was free of PET-avid uptake.

Results: Of this cohort of 84 patients, 24 had at least one pelvic node or metastatic site disease, 1 to 13 lesions per patient, with a total of 98 lesions (60 pelvic nodes/38 extra-pelvic nodal diseases and haematogenous metastases). Target volumes ranged from 0.08 to 9.6 cm^3 while SUVmax ranged from 2.1 to 55.0. nSUV ranged from 1.9 to 15.7/2.4 to 25.7/2.5 to 34.5 for the 5 mm/10 mm/20 mm shell expansion. Furthermore, 74%/68%/34% of the lesions had nSUV ≥ 3 and were free of PSMA PET uptake inside the GTV outer shell margin expansion of 5 mm/10 mm/20 mm. Adjacent avid organs were another lesion, bladder, bowel, ureter, prostate, and liver.

Conclusions: The majority of PSMA PET/CT-defined radiotherapy targets would be suitable for BgRT by using a 10-mm tracking zone in prostate cancer. A subset of lesions had adjacent non-tumour uptake, mainly due to the proximity of ureter or bladder, and may require exclusion from emission tracking during BgRT.

Keywords: BgRT, PSMA, oligometastasis, prostate, BTZ

INTRODUCTION

Biology-guided radiotherapy (BgRT) is a novel therapeutic modality that intends to guide radiation therapy using functional imaging such as positron emission tomography (PET) (1–3). A linear accelerator incorporating dual 90° PET detectors (PET-linac) has been developed to perform real-time PET image guidance and spatial tracking (RefleXion Medical, Hayward, USA) (4, 5). The PET-linac is equipped with a 6-MV flattening filter-free (FFF) photon beam with a nominal dose rate of 8.5 Gy/min. Dose is delivered by a rotating ring-shape gantry (60 RPM) with an 85-cm bore diameter. The linac includes a multi-leaf collimator (MLC) of 64 leaves, a kVCT imaging system able to acquire 3D CT fan-beam images, a mega-voltage detector array opposite to the linac head, and a 6-degrees-of-freedom couch. The PET-linac may be used to deliver intensity-modulated radiotherapy (IMRT), stereotactic surgery (SRS), and stereotactic ablative radiation therapy (SABR). During BgRT treatment, detection of annihilation photons originating from a volume called the biological tracking zone (BTZ) triggers the delivery of beamlets of radiation to the lesion with sub-second latency. The BTZ ensures that detection of non-target positron emission is minimized. Only the PET signal coming from the BTZ triggers delivery during BgRT.

Prostate-specific membrane antigen (PSMA)-targeted PET tracers have recently been developed for imaging of primary and metastatic prostate cancer (6–11). PSMA PET has been associated with superior specificity and sensitivity compared with conventional imaging (12, 13). Due to its highly specific uptake, there is significant interest in PSMA PET for BgRT of prostate metastases based on PSMA PET.

SABR has been successfully used to treat oligometastatic prostate cancer (OMPC) with excellent local control and minimal toxicity (14–19). There is increasing evidence that delivering ablative doses of radiotherapy to oligometastases can lead to improved survival and ongoing studies are currently evaluating the potential benefit of ablative radiotherapy to polymetastatic diseases (5, 20, 21). BgRT may be ideally suited to the complex task of delivering ablative radiotherapy to polymetastases due to its potential to efficiently treat many lesions in a single session, as well as real-time tracking of tumour motion, which could lead to better sparing of normal tissue (22, 23).

The feasibility of BgRT for OMPC was addressed through a recent planning study (24). It was found that target coverage and conformity were similar between BgRT plans and clinical SABR plans and that BgRT could have efficiency gains because of unified motion management for all lesions.

The goal of this study is twofold. First, we aim to describe disease distribution in synchronous OMPC and synchronous polymetastatic prostate cancer in terms of number of nodal and distant metastases per patient and anatomical location. Second, we aim to characterize the standardized uptake value (SUV) of lesions and their surroundings in order to determine the proportion of lesions that may be suitable for BgRT treatment.

MATERIALS AND METHODS

This is a retrospective analysis of PSMA PET/CTs acquired at our institution of patients enrolled in the ProPSMA prospective randomized trial (ID ANZCTR12617000005358) (25, 26). In this trial, patients with high-risk prostate cancer underwent Gallium-68 (^{68}Ga) PSMA-11 PET/CT at the time of diagnosis. PET/CT scans were performed with the Discovery PET/CT 690 or 710 (General Electric Medical System, Milwaukee, USA). The PET/CT resolution was 2.9 mm × 2.9 mm × 3.27 mm/1.1 mm × 1.1 mm × 3.27 mm. Lesion identification, node/metastasis classification, and disease staging were assessed by nuclear medicine physicians at the time of diagnosis. Since the ProPSMA clinical trial was a staging study, no radiotherapy planning CTs were acquired for these patients. All patients were androgen deprivation therapy (ADT)-naïve at the time of acquisition.

Guided by the PSMA uptake on PET, nodal or distant metastases were contoured on the CT component of PET/CT by a genitourinary radiation oncologist as gross tumour volume (GTV). This workflow differs from the primary intent of the BgRT workflow where lesions would first be delineated on the planning CT and then the planning CT would be registered to the CT component of a PET/CT scan (4, 5). Segmentation was performed by using the Eclipse treatment planning system (v15.06, Varian Medical Systems, Palo Alto, USA). Lesions were further classified into anatomical categories depending on their location to assess their distribution. Misregistration between the CT component and PET can occur due to a combination of factors including patient movement, respiratory motion, or physiologic movements. If this was the case, the avid region on PET was registered manually to the contour on CT.

The PET signal detected during BgRT treatment must come from the lesion and not from other physiological activity surrounding the lesion to offer reliable spatial tracking. Ideally,

a lesion would be isolated from any other physiological activity to be suitable for BgRT. The normalized SUV (nSUV) was calculated to characterize the PET signal. nSUV was defined as the ratio of SUVmax inside the GTV to SUVmean inside an isotropic outer shell margin expansion of the GTV excluding the GTV itself. nSUV is similar to the so-called tumour-to-background ratio (TBR) (27, 28). SUV was normalized by patient body weight to allow for interpatient comparison. ^{68}Ga SUV quality control was embedded in the ProPSMA study (29).

The BTZ was the volume resulting from the union of the GTV and the outer shell margin expansion of the GTV. BTZ sizes may vary depending on the lesion size and location. To model the impact of different BTZ sizes, outer shell expansions of 5 mm/10 mm/20 mm were considered. It was assumed that only one lesion could be treated per BTZ.

A lesion may be suitable for BgRT if nSUV is larger than a specific nSUV threshold value; however, the value of the nSUV threshold has not been established for PSMA PET. Potential nSUV threshold values were studied by calculating the cumulative probability distribution function of nSUV to be larger than an nSUV threshold for a lesion. The calculation was repeated for outer shell GTV margin expansions of 5 mm/10 mm/20 mm. Results obtained with nSUV threshold = 3 were explicitly reported in this study for illustration purposes.

A lesion may have nSUV larger than the nSUV threshold but not be suitable for BgRT as high physiological uptake in the BTZ may be averaged out in the determination of SUVmean. Physiological activity inside the BTZ may originate from another avid lesion or from an organ at risk (OAR). To quantify the distance between the neighbouring avid region and the GTV, spherical shells of 3-mm thickness resulting from an outer shell expansion of the GTV were grown at a distance *d* between the outer layer of the shell and the GTV, where *d* ranged from 3 to 50 mm with a 1-mm step size. SUVmax inside these shells as a function of the distance was reported. The proportion of lesions for which SUVmax decreased continuously in a given length interval as a function of the distance from the GTV was determined, and these lesions were designated as isolated lesions. The classification of isolated lesions was repeated by considering uptake increase in 1 to 5 consecutive shells. The optimal number of consecutive shells to consider was determined by manually comparing results with the actual SUV distribution as seen on the PET/CT images. Only SUVmax larger than 1 was considered in the calculation. Outer shell expansions of the GTV and SUV extraction were performed with the MIM software (v6.9.4, MIM Software Inc., Cleveland, OH).

A lesion was considered suitable for BgRT if (1) nSUV was larger than an nSUV threshold and (2) adjacent non-tumour tissue was free of PSMA PET uptake inside the outer shell expansion. Since the value of the nSUV threshold and shell thickness may be variable in the PET-linac system, the nSUV threshold from 2 to 6 and shell expansion with thickness of 5 mm/10 mm/20 mm were reported in this study.

Differences between distributions were characterized by using the Wilcoxon rank-sum test. The null hypothesis that medians are similar was rejected at the 95% statistical level. Furthermore, statistical correlations were calculated by using the Spearman correlation coefficient (r_s) and its associated p-value.

RESULTS

Over the whole patient cohort, PSMA PET/CTs for 84 patients were acquired at our institution. Twenty-four (29%) of these patients had at least one pelvic nodal or one distant metastasis. In these, 98 lesions were segmented, resulting in 60 pelvic nodal diseases (N1) and 38 extra-pelvic nodal diseases and haematogenous metastases (M1).

The most common diagnosis involved at least one node or one metastases (N1M1), which was found in 12 (14%) patients. Twenty (24%) patients had nodal disease (N1M0+N1M1), and 16 (19%) patients had metastatic disease (N0M1+N1M1). This patient distribution was representative of the complete ProPSMA clinical trial cohort [N1M1+N0M1+N1M0: 30.0%, N1M0 +N1M1: 25%, N0M1+N1M1: 16%, n = 295 (26)] and similar to another prostate cancer staging study [N1M1+N0M1+N1M0: 32%, N0M1+N1M1: 16%, n = 134 (30)].

The distribution of lesions per patient is shown in **Figure 1**. The number of lesions per patient ranged from 1 to 13 lesions, with a median number of 3 lesions per patient. Three patients had more than 10 lesions, and five patients had only 1 lesion. The lesions were further classified into nine categories depending on their anatomical location. The anatomical details of each category are shown in **Table 1**. Lesions were mostly located in the iliac and in the common iliac (52% of all lesions) stations. In addition, a high number of lesions were found in the mesorectum (13%) and in the para-aortic (10%) basin in this population.

The median three-dimensional registration shift between the CT component and the PET component was less than the PET resolution (median 3D shift = 2.0 mm, interquartile range = 1.3–2.8 mm). Lesion volumes ranged from 0.08 to 9.6 cm^3 with a median (interquartile range) of 0.76 cm^3 (0.38–1.4 cm^3). The difference in volume between the pelvic nodes and the metastases was not statistically significant (p-value = 0.16). SUVmax ranged from 2.1 to 55.0 with median (interquartile range) = 8.6 (4.8–18.0). The SUVmax distribution of pelvic nodes and distant metastases was similar (p-value = 0.60). A positive correlation was observed between SUVmax and the lesion volume (r_s = 0.5, p-value < 10^{-7}). The correlation was stronger for the pelvic nodes only (r_s = 0.6, p-value < 10^{-6}) as compared with metastases only (r_s = 0.5, p-value < 10^{-2}). The calculation was repeated for all anatomical sites. The correlation was statistically significant only in iliac nodes (r_s = 0.65, p-value < 10^{-5}, n = 40) and bone metastases (r_s = 0.83, p-value = 0.01, n = 8).

An illustration of GTV contour on the CT component and its corresponding GTV outer shell margin expansion on the PET component used to determine nSUV is shown in **Figures 2A, B**. The distribution of nSUV calculated for the outer shell margin expansion of 5 mm/10 mm/20 mm is further shown in **Figure 2C**. nSUV increased from a 5-mm margin expansion to a 10-mm margin expansion (p-value < 10^{-4}) and from a 10-mm margin expansion to a 20-mm margin expansion (p-value =

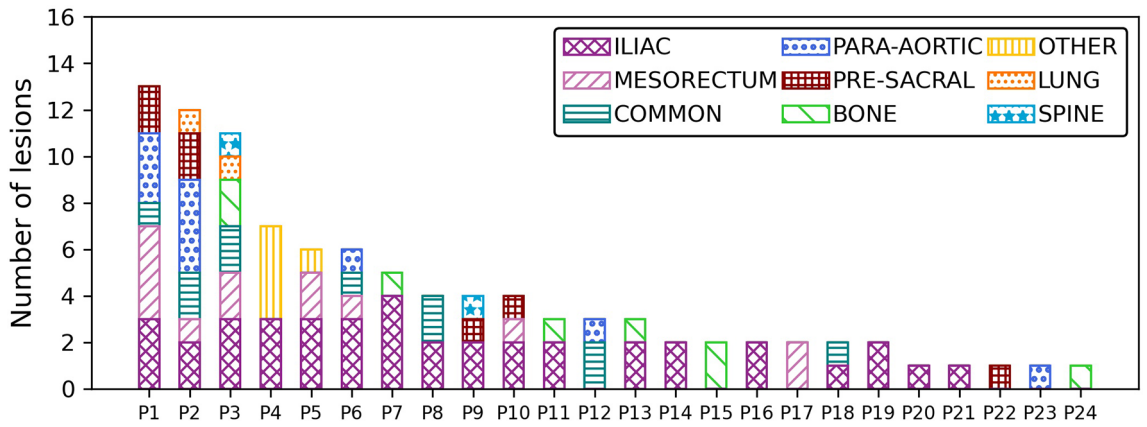

FIGURE 1 | Lesion distribution per anatomical site for the ProPSMA patient cohort.

0.02) (nSUV = 4.0 (3.1–6.2)/5.7 (3.8–10.3)/7.1 (4.2–14.3), for 5 mm/10 mm/20 mm shell thickness).

The cumulative probability distribution of lesions having nSUV greater or equal to a nSUV threshold as a function of the nSUV threshold is shown in **Figure 2D** for the three outer shell expansions considered. In particular, 76%/88%/93% of the lesions have nSUV ≥ 3 by using a shell expansion of 5 mm/10 mm/20 mm.

Examples of spherical shells of fixed 3-mm thickness with the outer layer located at 10 mm/20 mm/30 mm from the GTV are shown in **Figures 3A, C, E** while the extracted SUVmax inside the shell as a function of the distance between the outer layer of the shell and GTV is shown in **Figures 3B, D, F**, respectively. **Figures 3A, B** show an example of an isolated lesion for all distances. However, the bladder was located within the first 10 mm from the GTV in **Figure 3C** and SUVmax increased at distances larger than 6 mm from the GTV, as shown in **Figure 3D**. The ureter was located in the first 5 mm from the GTV in **Figure 3E**, and SUVmax is either increasing or is constant in the first 15 mm from the GTV in **Figure 3F**.

The optimal results to determine if lesions were isolated from any other uptake were obtained when considering a SUVmax increase in two consecutive shells. The ureters were the main avid region near lesions located in the iliac and common iliac (52% of all lesions). The bladder was located at distances larger than 20 mm for lesions in the mesorectum and in other nodes (18% of all lesions). Furthermore, the bowel or another avid lesion was within 15 mm for lesions located in the para-aortic region and in the pre-sacral region (17% of all lesions). Finally, lesions located in the lung, spine, and bone (12% of all lesions) were the most isolated from any other PET signal for all distances.

The proportion of lesions suitable for BgRT is shown in **Figure 4**. By using nSUV ≥ 3, 74%/68%/34% of the lesions was suitable for BgRT inside a distance of 5 mm/10 mm/20 mm from the GTV, respectively. The proportion of lesions suitable for BgRT decreased as the threshold was increased; 33%/49%/30% of the lesions was isolated from the adjacent non-tumour uptake and satisfied nSUV ≥ 5 inside the GTV margin expansion of 5 mm/10 mm/20 mm.

DISCUSSION

BgRT aims at localizing radiotherapy delivery based on biological features and incorporating this information for radiotherapy delivery, simplifying the process of irradiation to multiple sites of disease throughout the body (4, 5). In the context of increasing

TABLE 1 | Category used to classify the anatomical location of lesions together with the number of lesions found for each category.

	Category	Anatomical location	Number of lesions
1.	ILIAC	Internal, external, obturator	40
2.	MESORECTUM	Mesorectum	13
3.	COMMON	Common iliac	11
4.	PARA-AORTIC	Para-aortic, interaortocaval	10
5.	PRE-SACRAL	Pre-sacral	7
6.	BONE	Ramus, femur, rib, acetabular	8
7.	OTHER	Inguinal, epigastric	5
8.	LUNG	Intrathoracic, lung	2
9.	SPINE	L3	2

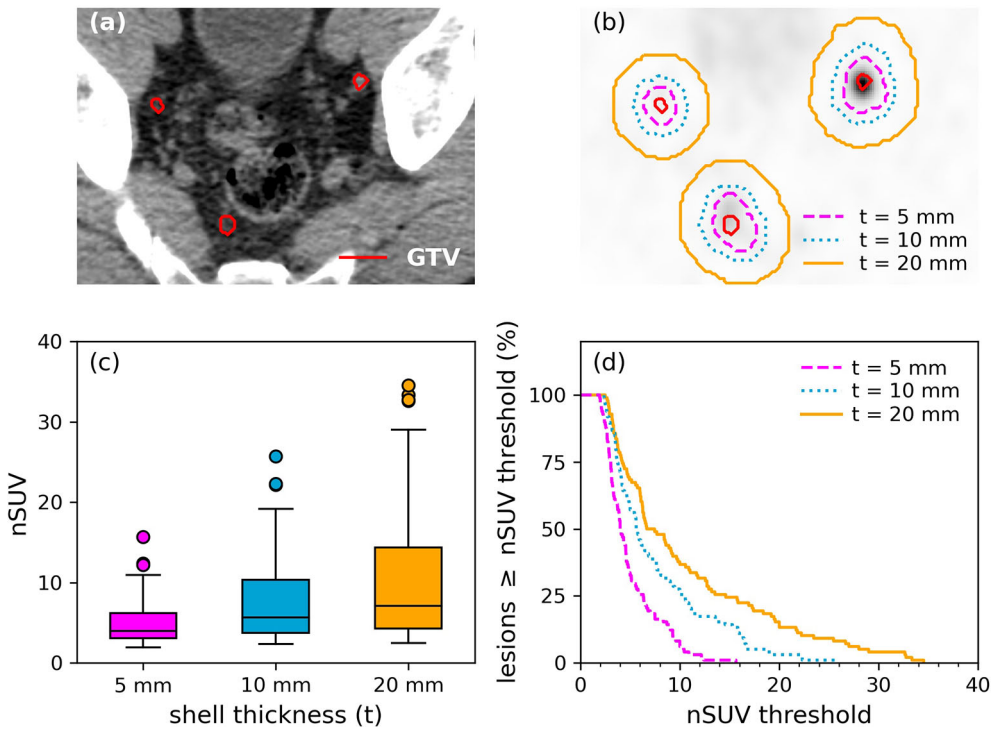

FIGURE 2 | Illustration of lesions for a patient. **(A)** GTVs (red) were segmented on the CT component while **(B)** outer shell expansion was performed on the PET component. Outer shells resulting from a margin expansion of 5 mm/10 mm/20 mm are shown. **(C)** Distribution of nSUV by using an outer shell margin expansion of 5 mm/10 mm/20 mm. **(D)** Cumulative probability distribution function of lesions having nSUV greater or equal to an nSUV threshold as a function of the nSUV threshold. Results inside a shell thickness of 5/10/20 mm are shown.

evidence for ablative radiotherapy for oligometastatic disease, BgRT has a potential role for efficient therapy of metastatic disease in the future (18, 21, 31).

In order to evaluate the feasibility of BgRT in the setting of synchronous oligo- and poly-metastatic metastatic prostate cancer, an anatomical description of the disease for patients enrolled in the ProPSMA clinical trial at our institution was reported. Several BTZ sizes and nSUV thresholds were considered as these parameters may be varied in PET-linac settings.

We have demonstrated that the majority of metastatic targets would have a satisfactory BTZ with a clearly defined tumour. Another lesion, the bladder, or the ureter was commonly found in the surrounding of the lesion. Use of the ^{18}F-PSMA-1007 PET tracer which offers a lower urinary clearance and a longer half-life may help to reduce uptake originating from the bladder and the ureter and increase the proportion of lesions suitable for BgRT (32, 33).

Lesions located in the lung, spine, and bone were more isolated from adjacent PET signals when compared with other sites for all distances, suggesting that these locations are optimal candidates for BgRT. However, these locations were less prevalent, representing only 10% of all lesions in this cohort. Lung lesions would benefit from BgRT due to real tracking of lesion motion if margins would be reduced. Spine and bone lesions may benefit from BgRT if the potential of treating multiple lesions in a single session would lead to a significant reduction in the treatment time as compared with an image-guided SABR approach.

This study focused on an early step on the developmental pathway of BgRT treatment, namely, how many lesions would be suitable for BgRT and in what clinical situation. Further steps would be required prior to clinical implementation, which may include the integration of PET in the simulation, treatment planning, and dose calculation processes and determination of the fidelity of the PET distribution immediately before treatment.

There were limitations in this study. First, since the ProPSMA dataset was a staging study, no planning CT was available for this patient cohort. The diagnostic CT component of a PET/CT scan was used to perform the segmentation. This step is not expected to be part of a typical BgRT workflow as a planning CT would be required for delineation. Additional challenges are therefore expected in the BgRT workflow such as accurate registration between the planning CT and the CT component of the PET/CT considering potential changes in anatomy between the two acquisitions or different spatial resolution between the two datasets.

Only one lesion per BTZ was assumed. However, it may be possible to treat multiple lesions inside the BTZ if conditions to suitability are met. Such treatment would increase the number of lesions suitable of BgRT determined in this study since the number of lesions free from adjacent PSMA PET uptake was determined regardless of the source of the PET signal.

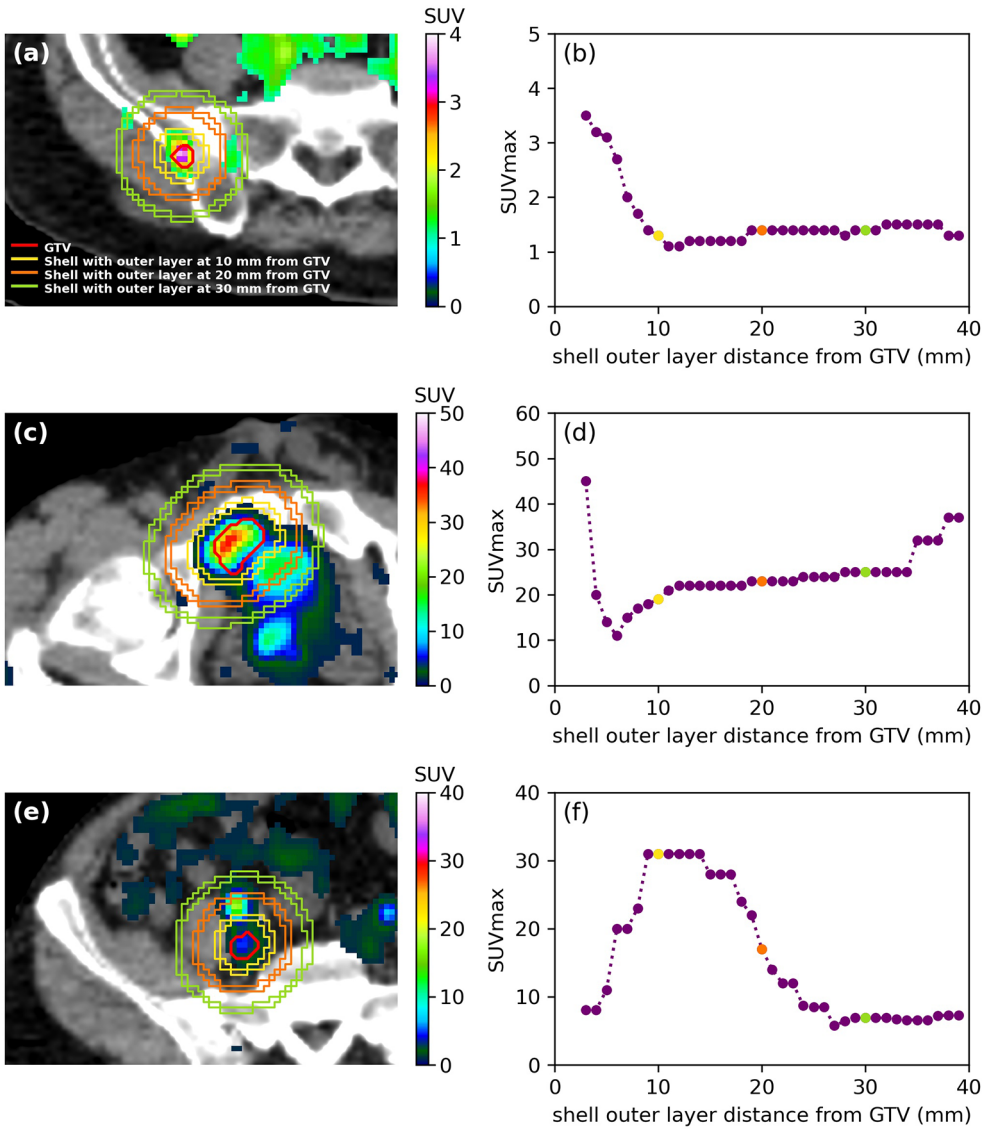

FIGURE 3 | **(A, C, E)** SUV distribution and illustration of the shell method to extract SUVmax for three different patients as well as **(B, D, F)** resulting SUVmax as a function of the distance of the outer later from the GTV (mm). Only SUV > 1 is shown for clarity. **(A)** The lesion was isolated from any other functional region, and **(B)** SUVmax decreased or was constant. **(C)** The bladder was located within 10 mm of the lesion, and **(D)** SUVmax increased in the first 5 mm from the lesion. **(E)** The ureter was in the first 5 mm from the lesion, and **(F)** SUVmax increased up to 15 mm away from the lesion.

It was further assumed that nSUV remained constant from the BgRT planning session to the treatment. nSUV may vary during this period, as observed with androgen deprivation therapy (ADT) (34, 35), and a lesion judged suitable for BgRT during the planning session may not satisfy the suitability conditions at the treatment day. Further studies may assess nSUV robustness through time.

Finally, misregistration between the CT component and the PET component was corrected manually on a per-lesion basis. Misregistration due to patient movement, respiratory motion, and physiological motion is expected to happen during BgRT treatment, and consequently, results presented in this study represent a case scenario where all of the above are accounted for.

CONCLUSIONS

Suitable pelvic nodal and distant metastases for BgRT were identified in this retrospective study for patients with synchronous oligometastatic and synchronous polymetastatic prostate cancer. These lesions are characterized with a high-intensity PET signal inside the GTV and a low-intensity PET signal in their surroundings. Optimal candidates for BgRT were

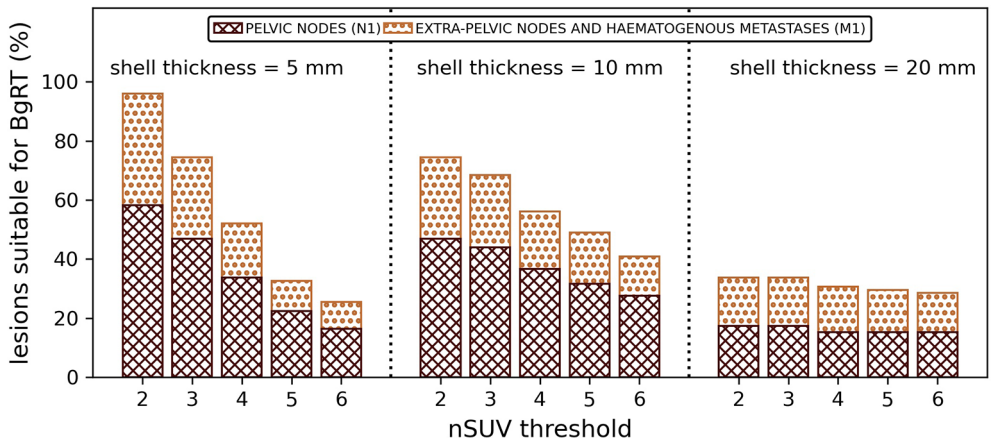

FIGURE 4 | Proportion of lesions (%) suitable for BgRT (nSUV ≥ nSUV threshold and free of PSMA PET uptake inside the GTV outer margin expansion) for several nSUV thresholds. Results per shell thicknesses are shown.

lesions located in the lung, spine, and bone. A subset of lesions had a neighbouring non-tumour uptake due to the proximity of an OAR, which may require exclusion from the biological tracking zone if this option if possible.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. MG and DC analysed and interpreted the patient data. MG performed the statistical analysis. All authors contributed to the manuscript revision and read and approved the submitted version.

FUNDING

This research is partially funded by RefleXion Medical. This work is also funded in part by the Peter MacCallum Cancer Centre Foundation. ProPSMA was an Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trial Group co-badged study by a clinical trial grant from the Prostate Cancer Foundation of Australia, funded by Movember. Shankar Siva is supported by the Victorian Cancer Council Colebatch Fellowship. MH is supported by a Challenge Award from the Prostate Cancer Foundation (PCF) supporting the Prostate Cancer Theranostics and Imaging Centre of Excellence (ProsTIC); funding was from Canica AS, Oslo, Norway. The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

REFERENCES

1. Evans PM. Anatomical Imaging for Radiotherapy. *Phys Med Biol* (2008) 53: R151–91. doi: 10.1088/0031-9155/53/12/R01
2. Verellen D, Ridder M, Storme G. A (Short) History of Image-Guided Radiotherapy. *Radiother Oncol* (2008) 86:4–13. doi: 10.1016/j.radonc.2007.11.023
3. Nestle U, Weber W, Hentschel M, Grosu AL. Biological Imaging in Radiation Therapy: Role of Positron Emission Tomography. *Phys Med Biol* (2009) 54: R1–25. doi: 10.1088/0031-9155/54/1/R01
4. Oderinde OM, Shirvani SM, Olcott PD, Kuduvalli G, Mazin S, Larkin D. The Technical Design and Concept of a PET/CT Linac for Biology-Guided Radiotherapy. *Clin Trans Radiat Oncol* (2021) 29:1–7. doi: 10.1016/j.ctro.2021.04.003
5. Shirvani SM, Huntzinger CJ, Melcher T, Olcott PD, Voronenko Y, Bartlett-Roberto J, et al. Biology-Guided Radiotherapy: Redefining the Role of Radiotherapy in Metastatic Cancer. *Br J Radiol* (2021) 94:20200873. doi: 10.1259/bjr.20200873
6. Cho SY, Szabo Z. Molecular Imaging of Urogenital Diseases. *Semin Nucl Med* (2014) 44:93–109. doi: 10.1053/j.semnuclmed.2013.10.008
7. van Leeuwen PJ, Stricker P, Hruby G, Kneebone A, Ting F, Thompson B, et al. 68Ga-PSMA has a High Detection Rate of Prostate Cancer Recurrence Outside the Prostatic Fossa in Patients Being Considered for Salvage Radiation Treatment. *BJU Int* (2016) 117:732–9. doi: 10.1111/bju.13397
8. Eiber M, Fendler WP, Rowe SP, Calais J, Hofman MS, Maurer T, et al. Prostate-Specific Membrane Antigen Ligands for Imaging and Therapy. *J Nucl Med* (2017) 58:67S–76S. doi: 10.2967/jnumed.116.186767
9. Hofman MS, Iravani A, Nzenza T, Murphy DG. Advances in Urologic Imaging: Prostate-Specific Membrane Antigen Ligand PET Imaging. *Urol Clinics North America* (2018) 45:503–24. doi: 10.1016/j.ucl.2018.03.016
10. Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-Specific Membrane Antigen PET: Clinical Utility in Prostate Cancer, Normal Patterns, Pearls, and Pitfalls. *Radiographics* (2018) 38:200–17. doi: 10.1148/rg.2018170108
11. Tosoian JJ, Gorin MA, Ross AE, Pienta KJ, Tran PT, Schaeffer EM, et al. And Treatment Considerations. *Nat Rev Urol* (2018) 14:15–25. doi: 10.1038/nrurol.2016.175

12. Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 Prostate-Specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer—Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-Specific Membrane Antigen-Avid Lesions: A Systematic Review and Meta-. *Eur Urol* (2020) 77:403–17. doi: 10.1016/j.eururo.2019.01.049
13. Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson D, et al. Diagnostic Performance of 18 F-DCFPyL-PET/CT in Men With Biochemically Recurrent Prostate Cancer: Results From the CONDOR Phase III, Multicenter Study. *Clin Cancer Res* (2021) 27:3674–82. doi: 10.1158/1078-0432.ccr-20-4573
14. Jereczek-Fossa BA, Beltramo G, Fariselli L, Fodor C, Santoro L, Vavassori A, et al. Robotic Image-Guided Stereotactic Radiotherapy, for Isolated Recurrent Primary, Lymph Node or Metastatic Prostate Cancer. *Int J Radiat Oncol Biol Phys* (2012) 82:889–97. doi: 10.1016/j.ijrobp.2010.11.031
15. Decaestecker K, de Meerleer G, Lambert B, Delrue L, Fonteyne V, Claeys T, et al. Repeated Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Recurrence. *Radiat Oncol* (2014) 9:1–10. doi: 10.1186/1748-717X-9-135
16. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, DeBruycker A, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol* (2018) 36:446–53. doi: 10.1200/JCO.2017.75.4853
17. Siva S, Bressel M, Murphy DG, Shaw M, Chander S, Violet J, et al. Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial. *Eur Urol* (2018) 74:455–62. doi: 10.1016/j.eururo.2018.06.004
18. de Bleser E, Jereczek-Fossa BA, Pasquier D, Zilli T, van As N, Siva S, et al. Metastasis-Directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-Institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. *Eur Urol* (2019) 76:732–9. doi: 10.1016/j.eururo.2019.07.009
19. Palma DA, Olson R, Harrow S, Gaede S, Louie A, Haasbeek C, et al. Stereotactic Ablative Radiotherapy Versus Standard of Care Palliative Treatment in Patients With Oligometastatic Cancers (SABR-COMET): A Randomised, Phase 2, Open-Label Trial. *Lancet* (2019) 393:2051–8. doi: 10.1016/S0140-6736(18)32487-5
20. Palma DA, Olson R, Harrow S, Correa RJM, Schneiders F, Haasbeek CJA, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4-10 Oligometastatic Tumors (SABR-COMET-10): Study Protocol for a Randomized Phase III Trial. *BMC Cancer* (2019) 19:816.1–15. doi: 10.1186/s12885-019-5977-6
21. Corkum MT, Fakir H, Palma DA, Nguyen T, Bauman GS. Can Polymetastatic Disease Be ARRESTed Using SABR? A Dosimetric Feasibility Study to Inform Development of a Phase 1 Trial. *Adv Radiat Oncol* (2021) 6:100734.1–6. doi: 10.1016/j.adro.2021.100734
22. Fan Q, Nanduri A, Mazin S, Zhu L. Emission Guided Radiation Therapy for Lung and Prostate Cancers: A Feasibility Study on a Digital Patient. *Med Phys* (2012) 39:7140–52. doi: 10.1118/1.4761951
23. Yang J, Yamamoto T, Mazin SR, Graves EE, Keall PJ. The Potential of Positron Emission Tomography for Intratreatment Dynamic Lung Tumor Tracking: A Phantom Study. *Med Phys* (2014) 41:021718.1-14. doi: 10.1118/1.4861816
24. Hrinivich WT, Phillips R, da Silva AJ, Radwan N, Gorin MA, Rowe SP, et al. Online Prostate-Specific Membrane Antigen and Positron Emission Tomography–Guided Radiation Therapy for Oligometastatic Prostate Cancer. *Adv Radiat Oncol* (2020) 5:260–8. doi: 10.1016/j.adro.2019.10.006
25. Hofman MS, Murphy DG, Williams SG, Nzenza T, Herschtal A, de Abreu Lourenco R, et al. A Prospective Randomized Multicentre Study of the Impact of Gallium-68 Prostate-Specific Membrane Antigen (PSMA) PET/CT Imaging for Staging High-Risk Prostate Cancer Prior to Curative-Intent Surgery or Radiotherapy (proPSMA Study): Clinical Trial Protocol. *BJU Int* (2018) 122:783–93. doi: 10.1111/bju.14374
26. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-Specific Membrane Antigen PET-CT in Patients With High-Risk Prostate Cancer Before Curative-Intent Surgery or Radiotherapy (proPSMA): A Prospective, Randomised, Multicentre Study. *Lancet* (2020) 395:1208–16. doi: 10.1016/S0140-6736(20)30314-7
27. Bois F, Noirot C, Dietemann S, Mainta IC, Zilli T, Garibotto V, et al. [68ga] Ga-PSMA-11 in Prostate Cancer: A Comprehensive Review. *Am J Nucl Med Mol Imaging* (2020) 10:349–74.
28. Zhao J, Hamm B, Brenner W, Makowski MR. Lesion-To-Background Ratio Threshold Value of SUVmax of Simultaneous [68Ga]Ga-PSMA-11 PET/MRI Imaging in Patients With Prostate Cancer. *Insights Into Imaging* (2020) 11:137.1-11. doi: 10.1186/s13244-020-00926-y
29. Bailey DL, Hofman MS, Forwood NJ, O'Keefe GJ, Scott AM, van Wyngaardt WM, et al. Accuracy of Dose Calibrators for 68Ga PET Imaging: Unexpected Findings in a Multicenter Clinical Pretrial Assessment. *J Nucl Med* (2018) 59:636–8. doi: 10.2967/jnumed.117.202861
30. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic Efficacy of 68Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients With Intermediate to High Risk Prostate Cancer. *J Urol* (2016) 195:1436–43. doi: 10.1016/j.juro.2015.12.025
31. Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol* (2020) 6:650–9. doi: 10.1001/jamaoncol.2020.0147
32. Rahbar K, Weckesser M, Ahmadzadehfar H, Schäfers M, Stegger L, Bögemann M. Advantage of 18F-PSMA-1007 Over 68Ga-PSMA-11 PET Imaging for Differentiation of Local Recurrence vs. Urinary Tracer Excretion. *Eur J Nucl Med Mol Imaging* (2018) 45:1076–7. doi: 10.1007/s00259-018-3952-0
33. Sprute K, Kramer V, Koerber SA, Meneses M, Fernandez R, Soza-Ried C, et al. Diagnostic Accuracy of 18F-PSMA-1007 PET/CT Imaging for Lymph Node Staging of Prostate Carcinoma in Primary and Biochemical Recurrence. *J Nucl Med* (2021) 62:208–13. doi: 10.2967/jnumed.120.246363
34. Ettala O, Malaspina S, Tuokkola T, Luoto P, Löyttyniemi E, Boström PJ, et al. Prospective Study on the Effect of Short-Term Androgen Deprivation Therapy on PSMA Uptake Evaluated With 68Ga-PSMA-11 PET/MRI in Men With Treatment-Naïve Prostate Cancer. *Eur J Nucl Med Mol Imaging* (2020) 47:665–73. doi: 10.1007/s00259-019-04635-7
35. Vaz S, Hadaschik B, Gabriel M, Herrmann K, Eiber M, Costa D. Influence of Androgen Deprivation Therapy on PSMA Expression and PSMA-Ligand PET Imaging of Prostate Cancer Patients. *Eur J Nucl Med Mol Imaging* (2020) 47:9–15. doi: 10.1007/s00259-019-04529-8

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
published: 14 April 2022
doi: 10.3389/fonc.2022.877452

Case Report: MR-Guided Adaptive Radiotherapy, Some Room to Maneuver

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Background: A magnetic resonance linear accelerator (MR-Linac) provides superior soft tissue contrast to evaluate inter- and intra-fraction motion and facilitate online adaptive radiation therapy (ART). We present here an unusual case of locally advanced castrate-resistant prostate cancer treated with high-dose palliative ultra-hypofractionated radiation therapy on the MR-Linac with significant inter-fraction tumor regression.

Case Presentation: The patient was a 65-year-old man diagnosed with metastatic prostate cancer to bone and pelvic lymph nodes 7 years prior. At diagnosis, he presented with a PSA of 23 ng/ml and was commenced on a luteinizing hormone-releasing hormone agonist, achieving a PSA nadir of 4.68 ng/ml at 12 months. The patient subsequently had progressive lower urinary tract symptoms, his PSA increased to 47 ng/ml, and there was a markedly enlarged pelvic mass involving the prostate with gross extra-capsular disease and invasion into the posterior bladder wall. The patient was referred for palliative radiation to the pelvic mass due to urinary symptoms, pain, and lower limb paraesthesia. Treatment was planned to be delivered on the MR-Linac with a schedule of 36 Gy over 6 weekly factions allowing for maximal target dose delivery while minimizing surrounding organs at risk (OARs) radiation exposure. Unexpectedly, the target volume had a marked 49% (453 cc to 233 cc) reduction that was accounted for in the online adaptive process. A new reference plan was generated after 3 fractions to add sacral plexus as an OAR, previously not visible due to mass encroachment. The patient reported ongoing reduction in urinary symptoms, pelvic pain, and lower limb paresthesia by the end of treatment.

Conclusion: Using daily MR-guided ART, improved visualization of the changing target and OARs ensured safe dose escalation. The unexpected positive response of the target and improved patient outcomes demonstrated the added value of the MR-Linac for online adaptive radiotherapy in this setting.

Keywords: MR-Linac, adaptive radiotherapy, prostate cancer, ultrahypofractionation, inter-fraction motion

OPEN ACCESS

Edited by:
Linda G. W. Kerkmeijer, Radboud University Nijmegen Medical Centre, Netherlands

Reviewed by:
Mariska Den Hartogh, Radiotherapiegroep, Netherlands
Raquel Bar-Deroma, Rambam Health Care Campus, Israel

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *16 February 2022*
Accepted: *16 March 2022*
Published: *14 April 2022*

Citation:
Li W, Winter J, Padayachee J, Dang J, Kong V and Chung P (2022) Case Report: Case Report: MR-Guided Adaptive Radiotherapy, Some Room to Maneuver. Front. Oncol. 12:877452. doi: 10.3389/fonc.2022.877452

INTRODUCTION

Image-guided radiation therapy (IGRT) enables the visualization, quantification, and correction of patient setup errors, monitoring changes to ensure high-quality dose delivery (1, 2). Recent advances in radiation therapy have introduced the clinical availability of a hybrid magnetic resonance linear accelerator (MR-Linac) to evaluate inter- and intra-fraction motion (3–5). Providing superior soft tissue contrast, these systems enable online adaptive radiation therapy (ART) to account for spatial and temporal anatomic changes to maximize dose to target while minimizing dose to surrounding organs at risk (OARs) (6, 7).

As prostate cancer is characterized by a low α/β ratio, hypofractionation or stereotactic body radiation therapy is increasingly prevalent to improve radiation efficacy while minimizing toxicity (8–10). The clinical implementation of hypofractionated prostate MR-Linac ART has been widely reported in the literature with promising early results (11–14). Though associated with a longer treatment session, use of ART with the MR-Linac enables tailored dose delivery to the target through re-contouring and re-planning activities prior to each fraction.

We present here an unusual case of a patient with metastatic castrate-resistant prostate cancer requiring palliative pelvic radiotherapy that resulted in large volume inter-fraction tumor regression that demonstrated a role of the MR-Linac in online adaptation.

CASE DESCRIPTION

The patient was a 65-year-old man diagnosed with metastatic prostate cancer to bone and pelvic lymph nodes 7 years prior. At the time of diagnosis, he presented with a prostate-specific antigen (PSA) of 23 ng/ml, and prostate biopsies confirming Gleason grade 4 + 5 = 9 disease with 12/12 cores involved and 80% overall involvement. Staging bone scan and CT thorax, abdomen and pelvis demonstrated multiple bone metastases and pelvic lymphadenopathy. The prostate was described as enlarged and heterogeneous with irregular margins. He commenced on a luteinizing hormone-releasing hormone (LHRH) agonist and achieved a PSA nadir of 4.68 ng/ml 1 year following androgen deprivation therapy (ADT) institution.

The patient subsequently had progressive lower urinary tract symptoms with nocturia x 5 and weak stream. His PSA had risen to 47 ng/ml and re-staging CT showed progressive bone metastases together with soft tissue disease and a 5.5-cm left adrenal metastasis. Additionally, there was a markedly enlarged pelvic mass centered on the prostate with gross extra-capsular extension and invasion into the posterior bladder wall (**Figure 1A**). Enzalutamide was commenced, with an initial

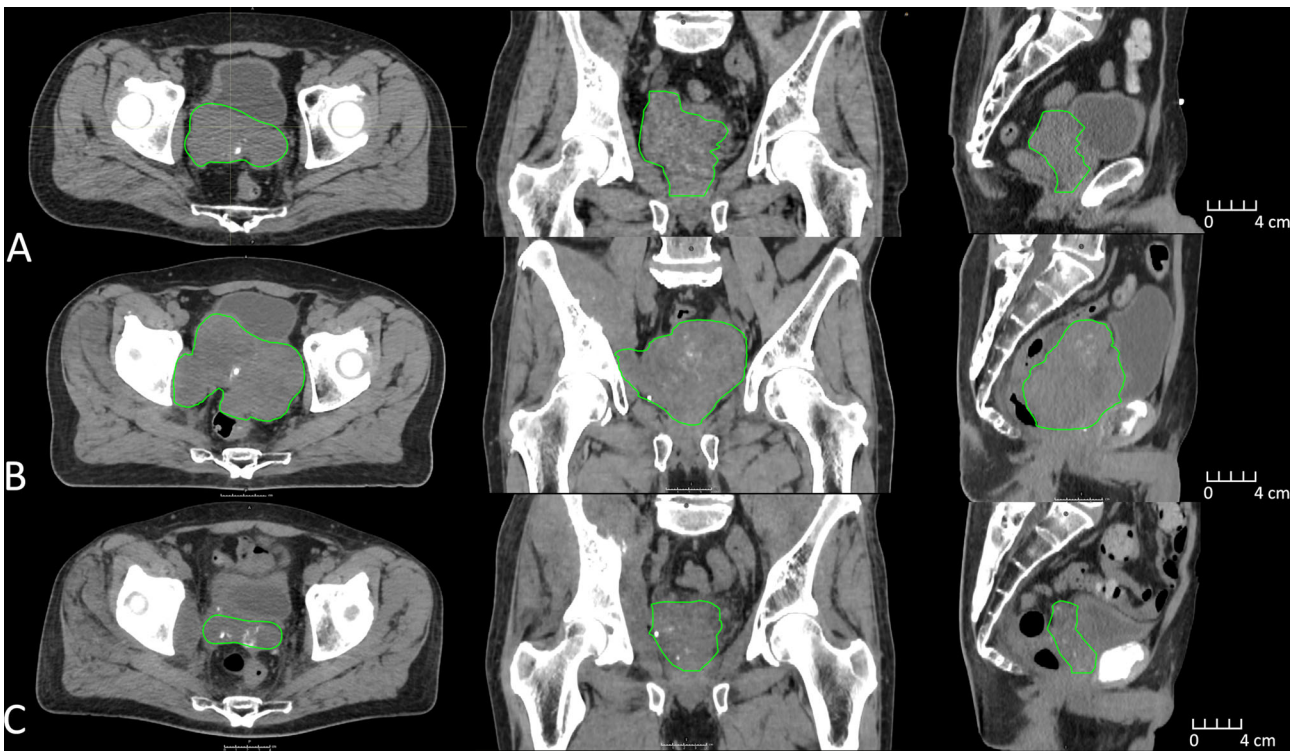

FIGURE 1 | CT imaging depicting clinical target volume (green) changes approximately 1 year prior to MR-Linac treatment **(A)**, immediately prior to MR-Linac treatment **(B)**, and 6 months post MR-Linac treatment **(C)**.

biochemical and radiological response. However, this was transient and within 4 months of commencing enzalutamide, PSA started rising again and peaked at 60 ng/ml associated with imaging progression. The imaging revealed multiple lobulated masses arising from the prostate encroaching onto the rectum, and new intramuscular masses in the right iliopsoas and right obturator internus (**Figure 1B**). Coinciding with this, the patient reported symptoms of pelvic pain and lower limb paresthesia. Enzalutamide was stopped and he was referred for palliative radiotherapy to the prostate. After discussion, it was agreed to proceed with radiotherapy, but as the mass was so large, it was felt that an ultra-hypofractionated approach might be beneficial. MR-Linac treatment was thought to offer the most ability to tailor radiotherapy delivery to maximize dose delivery but minimize dose to OARs.

The patient underwent both CT and MRI simulation session for treatment planning. A high-resolution T2-weighted MR image acquired on the Unity MR-Linac (Elekta Unity, Stockholm, Sweden) was used for reference planning, and the CT image was used to provide electron density information. The target (clinical target volume, CTV), bladder, rectum, and large bowel were contoured by the radiation oncologist (RO), and a planning target volume (PTV) was created using a 5-mm uniform expansion around the CTV. A reference plan of 36 Gy over 6 weekly factions was generated in the MR-Linac treatment planning system (Monaco v5.4, Elekta AB, Stockholm, Sweden) using a 9-field IMRT technique. The plan derived was purposefully heterogeneous allowing central tumor region dose escalation to 48 Gy. The OARs assessed included rectum, large bowel, and small bowel where dose constraints were strictly observed. The majority of the dose-escalated tumor mass was posterior–superior and no attempt was made to include the urethra in the dose-escalated volume. It was observed at fraction 2 that there had been substantial target volume reduction (17%) mostly in the superior and posterior directions. A new reference plan was generated after 3 fractions to add the sacral plexus contours and constraints (previously not visible due to mass encroachment) and also accounted for the changing tumor mass.

For each MR-Linac treatment session, a localization T2-weighted MR image (MR_{Loc}) was acquired. The reference plan was used as a starting point to generate an adapted plan based on the contours redefined in-session on the MR_{Loc} by the RO. While quality control checks, including secondary monitor unit verification and multi-disciplinary plan quality review on the adapted plan were performed, a verification MR (MR_{Ver}) was acquired to ensure the target was encompassed within the PTV. A third beam on MR (MR_{BO}) was acquired during radiotherapy beam on, which allowed assessment of the internal anatomy during treatment delivery. The patient completed the patient-reported outcome tool, Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP), prior to each treatment.

To determine the delivered dose for each treated fraction, the clinically treated daily adapted beams were computed on the MR_{BO}. To simulate the delivered dose without daily adaptation, we computed reference plan beams on the MR_{BO}. The delivered dose without daily adaptation using the initial reference plan for the first three fractions and the updated reference plan for the final three fractions were simulated. All images, structures, and dose distributions were exported to a separate treatment planning system for dose accumulation (Raystation v8, RaySearch, Stockholm, Sweden) using deformable image registration (DIR). To generate a high-quality DIR, manual contours were generated on the MR_{BO} images and these contours were used as controlling regions of interest (ROIs) for the hybrid intensity and structure-based DIR between the reference MR and each MR_{BO}. Following manual review of the DIR quality, dose for each adapted fraction as well as the simulated no-adaptation dose was deformed to the reference MR using the deformed vector field for evaluation on the reference MR.

The average MR-Linac treatment time was 64 min (range 59–77 min). Over the course of 6 fractions, the CTV decreased in volume from 453 to 233 cc (49%) (**Figure 2**). Using dose accumulation, the demonstrated cumulative dose to OARs was reduced with the use of daily adaptation compared with the simulated single offline adaptation (**Figure 3**). Both daily adaptation and offline adaptation provided sufficient target coverage, but with offline adaptation, target doses were greater than intended and exceeded the maximum dose to 1 cc clinical goal. Use of daily adaptation resulted in lower OAR doses as we were able to progressively spare the OARs as the target mass decreased (**Table 1**). In particular, dose reduction to the bladder, rectum, and large bowel was substantially reduced with use of online adaptation. There was a 16% reduction in D5cc bladder and 12% reduction in D20 rectum in plans with adaptation versus without adaptation.

Treatment was well tolerated with no patient-reported acute toxicities. Patient-reported outcomes collected through EPIC-CP indicated no worsening urinary and bowel symptoms throughout treatment. More so, urinary symptoms improved during treatment, corresponding with treatment response. The score for need to urinate frequently became a small problem by fraction 2, reduced to a very small problem by fraction 4, and resolved to no problems for fractions 5 and 6. The patient experienced very small problems with hot flashes and feeling depressed for the first 3 fractions, resolved to no problems for either factor over the last 3 fractions. Finally, the patient experienced a very small problem with a lack of energy for the first 4 fractions, increasing to a small problem on fraction 5, and moderate problem on fraction 6.

One month following radiation treatment, the patient's PSA reduced to 21 and there was evidence of partial radiological response within the prostate (**Figure 1C**). There was, however, progression within the intramuscular masses and left adrenal gland, which were not intentionally a part of the treatment target volume. Biopsies were obtained of the adrenal mass, which confirmed metastatic prostate adenocarcinoma. The patient was referred for consideration of systemic therapy clinical trials and underwent genetic testing as part of the assessment. He was found to carry a BRCA2 mutation, and was subsequently enrolled onto a randomized trial involving a PARP inhibitor.

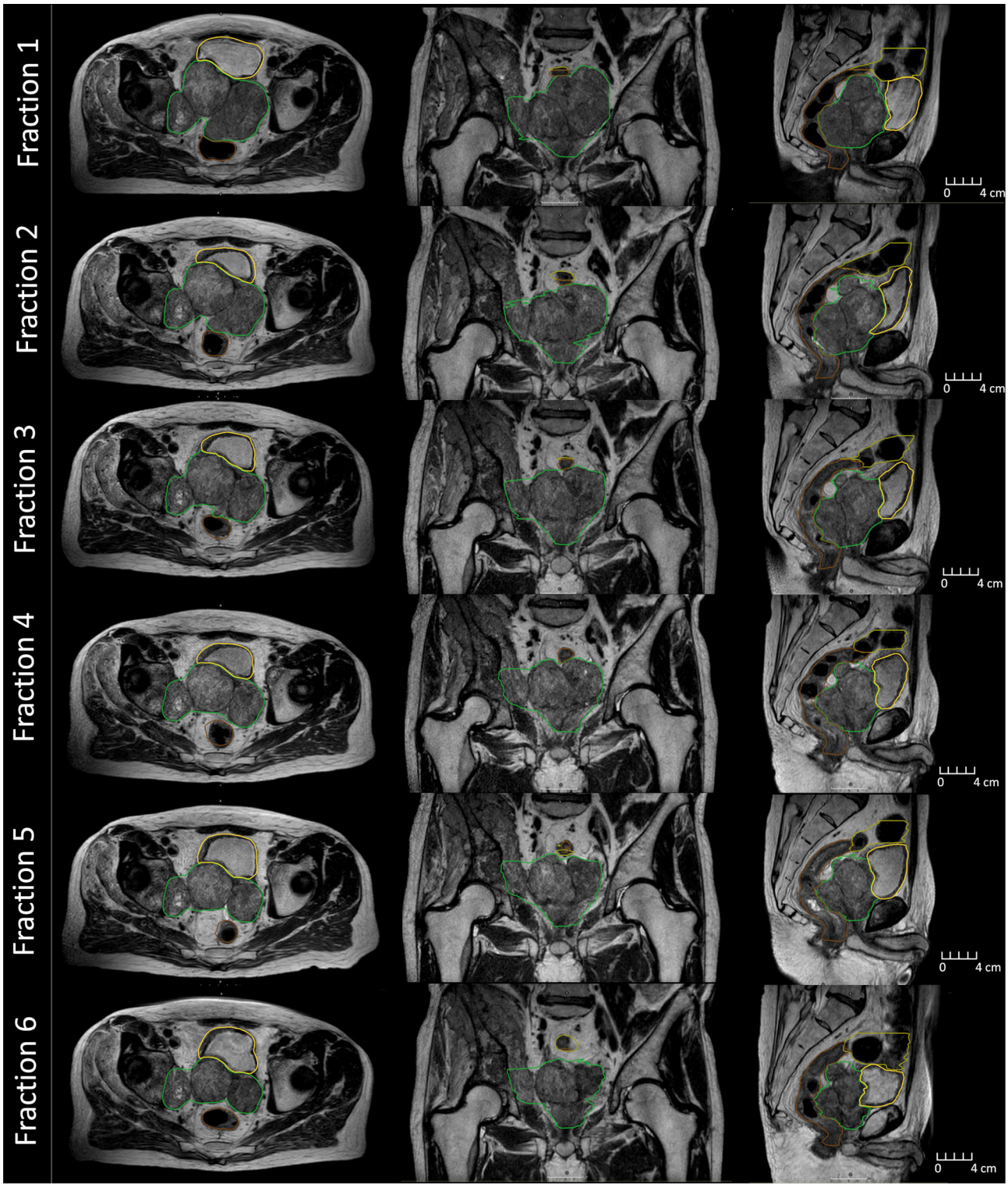

FIGURE 2 | MR images collected during beam delivery for each fraction on the MR-Linac during treatment. Displayed is the clinical target volume (green), rectum (brown), bladder (yellow), and large bowel (olive).

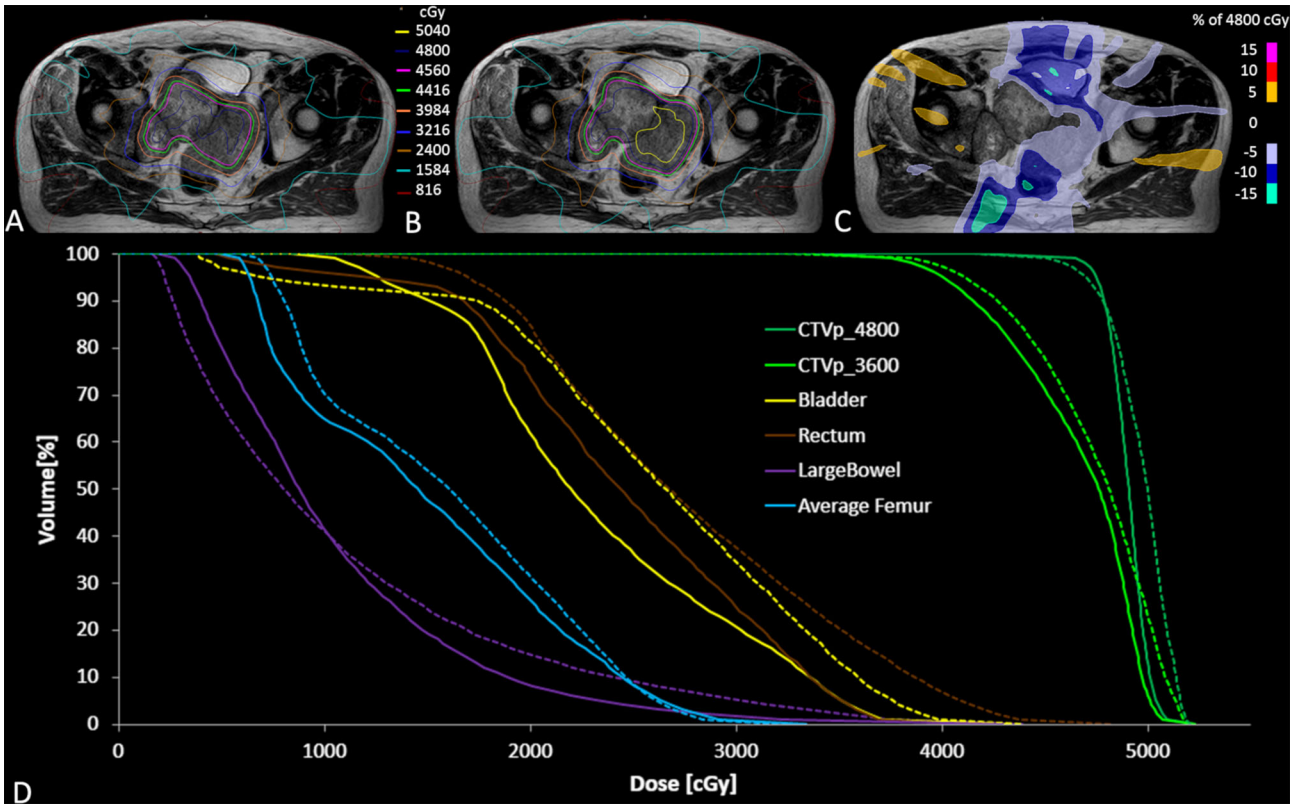

FIGURE 3 | Accumulated dose for all fractions on the reference MR scan for the clinically delivered treatment plan **(A)**, and simulated dose distribution without daily adaptation **(B)** along with the dose difference for the adapted plan minus non-adapted plan **(C)**. The accumulated DVH curves for both the adapted (solid lines) and non-adapted (dotted lines) are also illustrated **(D)**.

TABLE 1 | Comparison of key dose volume histogram (DVH) metrics between daily adapted and simulated workflow with single mid-treatment adaptation.

Region of Interest	DVH Metric	Clinical Goal (cGy)	Daily Adapted (cGy)	Simulated No Daily Adaptation (cGy)
CTVp_4800	D95	4,560	4,576	4,698
CTVp_3600	D99	3,420	3,570	3,849
CTVp_3600	D1cc	5,040	4,869	5,193
Rectum	D50	1,350	2,193	2,654
Rectum	D20	2,190	2,928	3,334
Rectum	D1cc	3,600	3,422	3,903
Bladder	D40	1,350	2,343	2,922
Bladder	D5cc	3,600	3,480	4,139
Left Femur	D5	1,520	1,967	2,058
Right Femur	D5	1,520	2,251	2,160
Large Bowel	D1cc	2,530	3,166	3,835
Left Sacral Plexus*	D1cc	1,800	1,510	1,792
Right Sacral Plexus*	D1cc	1,800	1,402	1,475

**Accumulated dose for the final 3 fractions reported, as the relevant region of the sacral plexus was only visible after fraction 3. Also note that the clinical goals were based on three fractions only.*

At the last follow-up, there was biochemical and radiological stability of disease.

DISCUSSION

Compared to conventional linac treatment, MR-guided daily ART provides improved target and OAR visualization with the ability to adapt radiation delivery to account for inter-fraction changes, enabling safe dose escalation. At our institution, one fractionation schedule for metastatic prostate cancer, where the goal of treatment is local pelvic tumor control, is based on one of two dose schedules used in the STAMPEDE trial 36 Gy in 6 weekly treatments (15). With MR-guided daily ART, the central target region in this patient was safely escalated to 48 Gy in an attempt to provide a higher probability of local control in the

large pelvic mass without increasing risk of toxicity. With the superior soft tissue contrast at each fraction, it was possible to visualize boundaries between CTV and OARs more clearly, as treatment progressed. This facilitated optimizing the therapeutic ratio, by maximizing target dose while minimizing OAR doses. On a conventional cone-beam CT (CBCT)-guided Linac, weekly changes in the target and OARs for this patient may not have been as readily observed.

Small target volume changes associated with prostate hypofractionation have previously been described with MR-Linac extreme hypofractionation (16, 17). In contrast, our patient had almost a 50% reduction in target volume, potentially due to the longer span in overall treatment time. The reduction may have also been associated with his BRCA2 mutation status as there are reports of increased radiosensitivity in normal and tumor cells of BRCA mutation carriers (18).

Determining the cost-effectiveness of novel radiation therapy technologies is important to balance cost versus perceived clinical benefits (19). The health economics for prostate MR-Linac treatments have been explored, where hypofractionated schedules did not show cost-effectiveness due to its high cost and lack of evidence to show substantial reduction in complications (20). As the current workflow for the MR-Linac involve a multidisciplinary team over a longer period of time when compared to conventional Linac treatment, one of the main implementation challenges is increased human-resource requirements (10, 21–23). Initiatives such as an oncologist-lite or therapist-led workflow to reduce human resource costs are being developed, but have yet to become mainstream practice (24–26). However, for this patient case, there were economic benefits and resource savings by treating him on the MR-Linac. Had the patient been treated on a conventional Linac with CBCT imaging, he may have triggered at least 1 iteration of replanning activity with the target size changes, even with the limited pelvic soft tissue contrast on CBCT. This replanning activity would have been resource intensive, involving the coordination of a new reference scanning session on the CT, recontouring of targets, creation of a new plan, additional physics and quality control checks, and potential delayed timelines for the patient.

There are several practical learnings in this case study to inform future use cases on the MR-Linac. First, temporal and spatial changes with the target and OARs may be difficult to predict in patients with large volume targets. With daily ART, it is possible to safely escalate dose beyond standard dose fractionation schemes to maximize impact on the target volume while minimizing OAR dose and associated toxicities. In this case, the central volume was escalated, but in the future, MR imaging biomarkers such as diffusion-weighted imaging estimates of the apparent diffusion coefficient and intra-voxel incoherent motion collected at each fraction offer potential for biological-based adaptive dose escalation. Second, this case demonstrates the value of the MR-Linac for palliative radiotherapy if target changes are expected, or unpredictable, over a course of treatment. The feasibility of palliative MR-Linac treatments have been explored to improve treatment efficiencies and reduce wait times (27). The unexpectedly large target response and positive cancer and toxicity outcomes supersedes the challenges related to longer treatment sessions and increased resource allocation associated with the MR-Linac. Finally, while the use of MRL appeared to be beneficial in this patient, it remains a relatively expensive, time-consuming treatment method. We would not routinely recommend this for all patients undergoing RT to the primary in the oligometastatic setting or in the setting or "standard" palliative radiotherapy. However, selective use in the situation where there are anticipated benefits in OAR sparing (particularly for ultrahypofractionated treatments) where challenging patient anatomy exists or, as experienced in our patient, large volume changes likely to benefit from adaptive RT may be the most appropriate indications.

PATIENT PERSPECTIVE

Prior to treatment, the patient reported pelvic pains and numbness in his toes. Following fraction 1, there was improvement noted in his presenting symptoms of pain and paresthesia, which completely abated by the end of the treatment course. Over the course of treatment, the patient was able to tolerate longer commutes without experiencing pain. Of note, the patient noted that mid-treatment, he was able to drive a long distance without the need for a break to enjoy a picnic with his wife.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University Health Network Research Ethics Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

WL wrote the first draft of the manuscript. JW, JP, and PC wrote sections of the manuscript. WL, JD, and VK contributed to image review and contouring. JW performed dose accumulation and generated figures. All authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

1. Jaffray DA. Image-Guided Radiotherapy: From Current Concept to Future Perspectives. *Nat Rev Clin Oncol* (2012) 9(12):688–99. doi: 10.1038/nrclinonc.2012.194
2. Bujold A, Craig T, Jaffray D, Dawson LA. Image-Guided Radiotherapy: Has it Influenced Patient Outcomes? *Semin Radiat Oncol* (2012) 22(1):50–61. doi: 10.1016/j.semradonc.2011.09.001
3. Winkel D, Bol GH, Kroon PS, van Asselen B, Hackett SS, Werensteijn-Honingh AM, et al. Adaptive Radiotherapy: The Elekta Unity MR-Linac Concept. *Clin Trans Radiat Oncol* (2019) 18:54–9. doi: 10.1016/j.ctro.2019.04.001
4. Lagendijk JJW, Raaymakers BW, van Vulpen M. The Magnetic Resonance Imaging–Linac System. *Semin Radiat Oncol* (2014) 24(3):207–9. doi: 10.1016/j.semradonc.2014.02.009
5. Mutic S, Dempsey JF. The ViewRay System: Magnetic Resonance–Guided and Controlled Radiotherapy. *Semin Radiat Oncol* (2014) 24(3):196–9. doi: 10.1016/j.semradonc.2014.02.008
6. Yan D. Adaptive Radiotherapy: Merging Principle Into Clinical Practice. *Semin Radiat Oncol* (2010) 20(2):79–83. doi: 10.1016/j.semradonc.2009.11.001
7. Sonke JJ, Aznar M, Rasch C. Adaptive Radiotherapy for Anatomical Changes. *Semin Radiat Oncol* (2019) 29(3):245–57. doi: 10.1016/j.semradonc.2019.02.007
8. Wang JZ, Guerrero M, Li XA. How Low is the Alpha/Beta Ratio for Prostate Cancer? *Int J Radiat Oncol Biol Phys* (2003) 55(1):194–203. doi: 10.1016/S0360-3016(02)03828-2
9. McPartlin AJ, Li XA, Kershaw LE, Heide U, Kerkmeijer L, Lawton C, et al. MRI-Guided Prostate Adaptive Radiotherapy – A Systematic Review. *Radiother Oncol* (2016) 119(3):371–80. doi: 10.1016/j.radonc.2016.04.014
10. Pathmanathan AU, van As NJ, Kerkmeijer LGW, Christodouleas J, Lawton CAF, Vesprini D, et al. Magnetic Resonance Imaging-Guided Adaptive Radiation Therapy: A "Game Changer" for Prostate Treatment? *Int J Radiat Oncol Biol Phys* (2018) 100(2):361–73. doi: 10.1016/j.ijrobp.2017.10.020
11. Raaymakers BW, Jurgenliemk-Schulz IM, Bol GH, Glitzner M, Kotte A, van Asselen B, et al. First Patients Treated With a 1.5 T MRI-Linac: Clinical Proof of Concept of a High-Precision, High-Field MRI Guided Radiotherapy Treatment. *Phys Med Biol* (2017) 62(23):L41–50. doi: 10.1088/1361-6560/aa9517
12. Alongi F, Rigo M, Figlia V, Cuccia F, Giaj-Levra N, Nicosia L, et al. 1.5 T MR-Guided and Daily Adapted SBRT for Prostate Cancer: Feasibility, Preliminary Clinical Tolerability, Quality of Life and Patient-Reported Outcomes During Treatment. *Radiat Oncol* (2020) 15(1):69. doi: 10.1186/s13014-020-01510-w
13. Bruynzeel AME, Tetar SU, Oei SS, Senan S, Haasbeek CJA, Spoelstra FOB, et al. A Prospective Single-Arm Phase 2 Study of Stereotactic Magnetic Resonance Guided Adaptive Radiation Therapy for Prostate Cancer: Early Toxicity Results. *Int J Radiat Oncol Biol Physics* (2019) 105(5):1086–94. doi: 10.1016/j.ijrobp.2019.08.007
14. Dunlop A, Mitchell A, Tree A, Barnes H, Bower L, Chick J, et al. Daily Adaptive Radiotherapy for Patients With Prostate Cancer Using a High Field MR-Linac: Initial Clinical Experiences and Assessment of Delivered Doses Compared to a C-Arm Linac. *Clin Trans Radiat Oncol* (2020) 23:35–42. doi: 10.1016/j.ctro.2020.04.011
15. Parker C, James N, Brawley C, Clarke N, Hoyle A, Ali A, et al. Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): A Randomised Controlled Phase 3 Trial. *Lancet* (2018) 392(10162):2353–66. doi: 10.1136/esmoopen-2018-000451
16. Gunnlaugsson A, Kjellen E, Hagberg O, Thellenberg-Karlsson C, Widmark A, Nilsson P. Change in Prostate Volume During Extreme Hypo-Fractionation Analysed With MRI. *Radiat Oncol* (2014) 9:22. doi: 10.1186/1748-717X-9-22
17. Clough A, Bridge P, Hales R, McDaid L, Choudhury A, Eccles CL. An Unusual Case of Oedematous Prostate Volumetric Changes Observed Over the Course of Radiotherapy on the MR Linear Accelerator. *J Med Imaging Radiat Sci* (2021) 52(1):147–51. doi: 10.1016/j.jmir.2020.11.019
18. Kim KH, Kim HS, Kim SS, Shim HS, Yang AJ, Lee JJB, et al. Increased Radiosensitivity of Solid Tumors Harboring ATM and BRCA1/2 Mutations. *Cancer Res Treat* (2022) 54(1):54–64. doi: 10.4143/crt.2020.1247
19. van Loon J, Grutters J, Macbeth F. Evaluation of Novel Radiotherapy Technologies: What Evidence is Needed to Assess Their Clinical and Cost Effectiveness, and How Should We Get it? *Lancet Oncol* (2012) 13(4):e169–77. doi: 10.1016/S1470-2045(11)70379-5
20. Hehakaya C, van der Voort van Zyp JRN, Vanneste BGL, Grutters JPC, Grobbee DE, Verkooijen HM, et al. Early Health Economic Analysis of 1.5 T MRI-Guided Radiotherapy for Localized Prostate Cancer: Decision Analytic Modelling. *Radiother Oncol* (2021) 161:74–82. doi: 10.1016/j.radonc.2021.05.022
21. van Herk M, McWilliam A, Dubec M, Faivre-Finn C, Choudhury A. Magnetic Resonance Imaging-Guided Radiation Therapy: A Short Strengths, Weaknesses, Opportunities, and Threats Analysis. *Int J Radiat Oncol Biol Phys* (2018) 101(5):1057–60. doi: 10.1016/j.ijrobp.2017.11.009
22. Hehakaya C, van der Voort van Zyp JR, Lagendijk JJW, Grobbee DE, Verkooijen HM, Moors EHM. Problems and Promises of Introducing the Magnetic Resonance Imaging Linear Accelerator Into Routine Care: The Case of Prostate Cancer. *Front Oncol* (2020) 10(1741). doi: 10.3389/fonc.2020.01741
23. Corradini S, Alongi F, Andratschke N, Belka C, Boldrini L, Cellini F, et al. MR-Guidance in Clinical Reality: Current Treatment Challenges and Future Perspectives. *Radiat Oncol* (2019) 14(1):92. doi: 10.1186/s13014-019-1308-y
24. Hales RB, Rodgers J, Whiteside L, McDaid L, Berresford J, Budgell G, et al. Therapeutic Radiographers at the Helm: Moving Towards Radiographer-Led MR-Guided Radiotherapy. *J Med Imaging Radiat Sci* (2020) 51(3):364–72. doi: 10.1016/j.jmir.2020.05.001
25. Willigenburg T, de Muinck Keizer DM, Peters M, Claes A, Lagendijk JJW, de Boer HCJ, et al. Evaluation of Daily Online Contour Adaptation by Radiation Therapists for Prostate Cancer Treatment on an MRI-Guided Linear Accelerator. *Clin Transl Radiat Oncol* (2021) 27:50–6. doi: 10.1016/j.ctro.2021.01.002
26. McNair HA, Joyce E, O'Gara G, Jackson M, Peet B, Huddart RA, et al. Radiographer-Led Online Image Guided Adaptive Radiotherapy: A Qualitative Investigation of the Therapeutic Radiographer Role. *Radiography (Lond)* (2021) 27(4):1085–93. doi: 10.1016/j.radi.2021.04.012
27. Benson R, Clough A, Nelder C, Pitt E, Portner R, Vassiliou M, et al. Evaluation of the Palliative Radiotherapy Pathway in a Single Institute: Can an MR Linac Improve Efficiency? *J Med Imaging Radiat Sci* (2022). doi: 10.1016/j.jmir.2021.11.010

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 22 April 2022
doi: 10.3389/fonc.2022.879089

Correlation Between Quantitative PSMA PET Parameters and Clinical Risk Factors in Non-Metastatic Primary Prostate Cancer Patients

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Edited by:
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University of Freiburg Medical Center, Germany

Reviewed by:
Kerstin Michalski,
University of Freiburg, Germany
Sebastian Hoberück,
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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: 18 February 2022
Accepted: 28 March 2022
Published: 22 April 2022

Citation:
Zschaeck S, Andela SB, Amthauer H, Furth C, Rogasch JM, Beck M, Hofheinz F and Huang K (2022) Correlation Between Quantitative PSMA PET Parameters and Clinical Risk Factors in Non-Metastatic Primary Prostate Cancer Patients. Front. Oncol. 12:879089. doi: 10.3389/fonc.2022.879089

Background: PSMA PET is frequently used for staging of prostate cancer patients. Furthermore, there is increasing interest to use PET information for personalized local treatment approaches in surgery and radiotherapy, especially for focal treatment strategies. However, it is not well established which quantitative imaging parameters show highest correlation with clinical and histological tumor aggressiveness.

Methods: This is a retrospective analysis of 135 consecutive patients with non-metastatic prostate cancer and PSMA PET before any treatment. Clinical risk parameters (PSA values, Gleason score and D'Amico risk group) were correlated with quantitative PET parameters maximum standardized uptake value (SUV_{max}), mean SUV (SUV_{mean}), tumor asphericity (ASP) and PSMA tumor volume (PSMA-TV).

Results: Most of the investigated imaging parameters were highly correlated with each other (correlation coefficients between 0.20 and 0.95). A low to moderate, however significant, correlation of imaging parameters with PSA values (0.19 to 0.45) and with Gleason scores (0.17 to 0.31) was observed for all parameters except ASP which did not show a significant correlation with Gleason score. Receiver operating characteristics for the detection of D'Amico high-risk patients showed poor to fair sensitivity and specificity for all investigated quantitative PSMA PET parameters (Areas under the curve (AUC) between 0.63 and 0.73). Comparison of AUC between quantitative PET parameters by DeLong test showed significant superiority of SUV_{max} compared to SUV_{mean} for the detection of high-risk patients. None of the investigated imaging parameters significantly outperformed SUV_{max}.

Conclusion: Our data confirm prior publications with lower number of patients that reported moderate correlations of PSMA PET parameters with clinical risk factors. With the important limitation that Gleason scores were only biopsy-derived in this study, there is no indication that the investigated additional parameters deliver superior information compared to SUV_{max}.

Keywords: PSMA, prostate specific membrane antigen, positron emission tomography, primary prostate cancer, quantitative PET parameters

INTRODUCTION

Various studies were able to show that Gallium-68-labelled prostate-specific membrane antigen (PSMA) positron emission tomography (PET) can improve nodal and distant staging of prostate cancer patients (1, 2). An additional benefit of PET imaging is that imaging parameters can be quantified, e.g., by the calculation of standardized uptake values (SUV), PSMA expressing tumor volume (PSMA-TV) and its derivatives. The maximum SUV (SUV_{max}) of tumor lesions has been shown to be prognostic for a plethora of diseases and tumor stages and various PET tracers, including the most commonly used tracer [^{18}F]fluorodeoxyglucose (FDG) but also less frequently used tracers (3, 4). Recent studies reported that (semi-)quantitative PSMA parameters appear to be a promising prognostic parameter. These investigations were mainly performed in advanced metastatic disease with patients prior to PSMA radioligand treatment (5, 6). In these cohorts of patients, high PSMA uptake seems to be associated with adverse outcome. So far, no data is available for locally confined disease and primary staging of prostate cancer, probably due to the relatively short follow-up time with this novel radiotracer.

Regarding focal radiotherapy treatment escalation in non-metastatic primary prostate cancer patients, an important issue is the potential correlation between quantitative PSMA ligand uptake measures and tumor aggressiveness, e.g. its correlation with the histopathological defined Gleason score. Additional PET parameters could help in the decision for more personalized treatment options like focal radiation boost to tumors, which has shown promising results in magnetic resonance imaging (MRI) guided boost delineation and is currently investigated in PSMA based focal dose escalation trials (7–9). Only weak to moderate correlation has been observed between PSMA PET SUV_{max} during initial staging of prostate cancer and Gleason scores obtained by biopsy. Similar modest correlations were reported for serum PSA values and SUV_{max} (2, 10, 11). Most studies only investigated SUV_{max} and did not analyse further quantitative PET metrics. A novel quantitative PET parameter is tumor asphericity (ASP). ASP is a measure of tumor shape irregularity and has shown a strong association with patient outcome in various diseases and for different PET tracers (12–15). In a recent study with a relatively small number of patients, ASP from [^{68}Ga]Ga-PSMA-11 PET was strongly associated with Gleason scores in patients with primary prostate cancer (16).

The aim of our study was to investigate the correlation between different quantitative PSMA parameters, including PSMA derived tumor volume (PSMA-TV) and ASP, with Gleason scores and PSA values and examine if one of these parameters outperforms SUV_{max}, especially regarding personalized treatment options of the primary tumour in patients without evidence of loco-regional or distant tumor lesions.

PATIENTS AND METHODS

Patient Cohort

For this retrospective analysis, all patients that underwent [^{68}Ga]Ga-PSMA-11 PET/CT imaging between January 2015 and December 2018 at a single tertiary hospital were screened for inclusion and exclusion criteria. Imaging findings and implications for staging of patients that were included until March 2018 have been previously published (17). For the current analysis, all additional consecutive patients with PSMA imaging until end of December 2018 were re-evaluated. Only treatment-naive patients without evidence for lymphonodal or distant metastases were included for further quantitative analyses. Since PSMA PET imaging is not part of the routine staging, referral for imaging was left at the discretion of the referring urologist or radiation oncologist. All except one patient had histologically confirmed prostate-cancer. The remaining patient had steadily rising PSA values during active surveillance, although repeated biopsies only revealed Gleason scores of 4. This patient was diagnosed with prostate cancer based on clinical findings (PSA increase, and characteristic findings in magnetic resonance imaging and PSMA PET/CT) and treated with radiotherapy.

Clinical Parameters

Clinical data were collected from patient files and electronic databases and included serological prostate-specific antigen (PSA) values, clinical T stage and Gleason scores obtained during biopsy prior to imaging. For a sub-group of patients that underwent surgery after PSMA PET imaging at the same institution, surgical Gleason scores were collected. Gleason scores were grouped following the recommendations of the 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma (18). Patients were allocated to low, intermediate, or

high-risk groups based on the established D'Amico risk classifier (19).

Image Acquisition

Imaging was performed as previously described (17). Briefly, PSMA PET/CT was performed with the radiotracer [^{68}Ga]Ga-PSMA-11-HBED-CC on a dedicated PET/CT scanner (Gemini TF 16; Philips, Netherlands) with Philips Astonish TF technology. [^{68}Ga]Ga-PSMA-11-HBED-CC was injected intravenously (median activity: 153 MBq; range: 71-227 MBq). PET imaging was performed after a median time of 98 minutes after injection (range: 39-188 minutes). Patients were placed in supine position and scanned from base of skull to the proximal femora (scan duration: 90 to 180 s per bed position; 3D acquisition mode; bed overlap: 53.3%). Attenuation correction was based on non-enhanced low-dose CT (automatic tube current modulation; maximum tube current-time product: 50 mA; tube voltage: 120 kV; gantry rotation time: 0.5 s) reconstructed with a slice thickness of 5 mm (convolution kernel: B08). PET raw data was reconstructed using iterative reconstruction with TOF analysis (Philips Astonish TF technology; BLOB-OS-TF; iterations: 3; subsets: 33). The projection data was reconstructed with 4 mm slice thickness (voxel size: 4×4×4 mm^3) (17).

Image Evaluation

In a first step, a large spheric mask was placed around the prostate and base of seminal vesicles. The PSMA expressing part of the primary tumor was delineated inside this mask based on a threshold of 41% SUV_{max} as suggested by a recent analysis (20). The resulting volumes of interest (VOI) were inspected visually by an experienced observer (SZ), and tracer uptake of surrounding normal tissue (bladder and/or rectum) was manually excluded. Patients who exhibited only low or diffuse tracer accumulation in the respective lesion were manually delineated by selecting the most intense single voxel, the volume in these patients was regarded 0.1 ml. This was the case in four patients.

For the obtained VOIs, ASP was computed according to the following formula, where V is the volume of the VOI and S is its surface.

$$ASP = \sqrt[3]{\frac{1}{36\pi}\frac{S^3}{V^2} - 1}$$

ASP is equal to zero for spheres. For non-spherical shapes ASP is higher than 0 and is a quantitative measure of the degree of deviation from a spherical shape.

In addition, the PSMA based tumor volume (PSMA-TV), the maximum standardized uptake value (SUV_{max}) and average standardized uptake value (SUV_{mean}) and SUV_{peak} were calculated. SUVs were computed using the patients body weight. All VOI definitions and image analyses were performed using the ROVER software, version 3.0.41 (ABX, Radeberg, Germany).

Statistical Analyses

The nonparametric Spearman correlation was used for calculation of correlations between imaging and clinical parameters to avoid bias due to existing outliers (as depicted in **Figures 1**, **2**). Receiver operating characteristics (ROC) curves were plotted to show sensitivity and specificity of each quantitative PET parameter for detection of high-risk prostate cancer (as defined by D'Amico criteria). Area under the curve (AUC) comparison between quantitative PET parameters were calculated using the DeLong test (MedCalc version 19.3, MedCalc Software Lt, Ostend, Belgium). All other statistical calculations and figure plots were performed using SPSS version 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Most patients had high-risk prostate cancer. **Table 1** summarizes clinical characteristics and quantitative imaging findings of the study cohort.

The investigated quantitative PSMA PET parameters were significantly inter-correlated with correlation coefficients between 0.20 and 0.95. The only exception was SUV_{mean} and ASP, which were not significantly correlated ($p = 0.79$). Details are shown in **Supplementary Table 1**. Regarding correlation between quantitative parameters of the primary tumor and clinical parameters, a significant, however low to moderate correlation with initial serum PSA values (Spearman rho between 0.19 and 0.45, all $p < 0.05$; **Table 2**; **Figure 1**) was observed. Correlation with Gleason scores obtained by previous biopsy was slightly lower (Spearman rho between 0.17 and 0.31, all $p < 0.05$ except for ASP; **Figure 2**).

Figure 3 shows the distribution of quantitative PET parameters for each Gleason score.

AUC analysis regarding the differentiation of high-risk from low- or intermediate-risk prostate cancer patients revealed poor to fair sensitivity and specificity for all investigated imaging parameters. AUC plots are depicted in **Figure 4** and the respective values are shown in **Table 3**. Comparison between AUC characteristics for different PET parameters showed that SUV_{max} is significantly better suited than SUV_{mean} to predict high-risk prostate cancer ($p = 0.035$), no significant differences between other quantitative metrics could be observed as shown in **Table 4**. Additionally, SUVpeak was investigated in the whole cohort, SUVpeak showed a very high correlation with SUVmax ($r = 0.99$, $p < 0.001$) and similar results regarding all investigated endpoints as shown in **Supplementary Figure 1**.

Since Gleason scores obtained from biopsy might over- or underestimate surgically obtained Gleason scores of whole prostate specimens, a sub-group of 38 surgically treated patients was further evaluated. Similar correlation coefficients as in the main analysis (but with each $p>0.05$) were obtained between quantitative imaging parameters and surgical Gleason scores (**Supplementary Table 2**, **Supplementary Figure 2**).

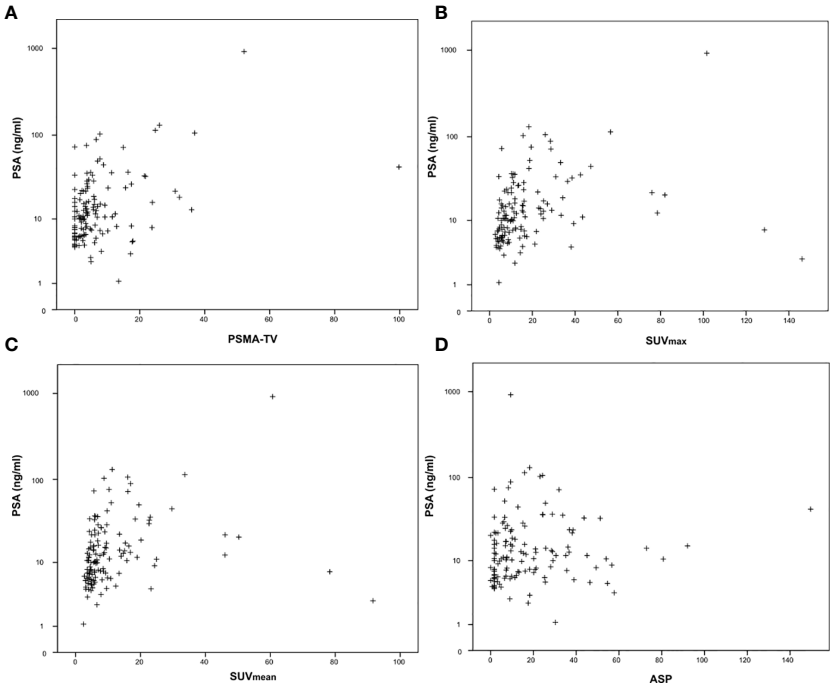

FIGURE 1 | Correlation between serum prostate-specific antigen (PSA) values and quantitative PSMA-PET parameters. **(A)** PSMA-derived tumor volume (PSMA-TV), **(B)** Maximum standardized uptake value (SUVmax), **(C)** Mean standardized uptake value (SUVmean) and **(D)** Tumor asphericity (ASP). PSA values are plotted on a logarithmic scale.

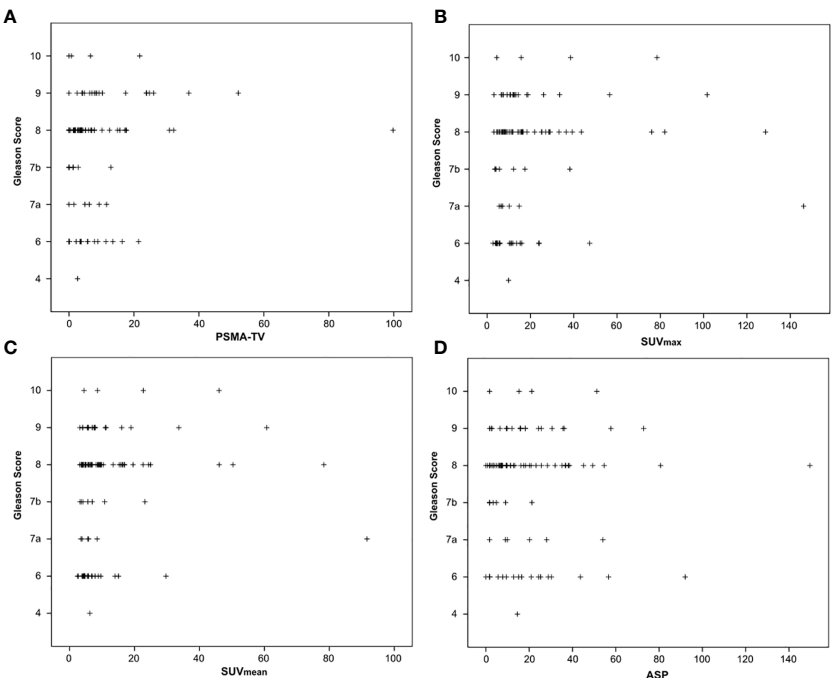

FIGURE 2 | Correlation between Gleason scores obtained by biopsy before imaging and quantitative PSMA-PET parameters. **(A)** PSMA-derived tumor volume (PSMA-TV), **(B)** Maximum standardized uptake value (SUVmax), **(C)** Mean standardized uptake value (SUVmean) and **(D)** Tumor asphericity (ASP).

TABLE 1 | Patient and PSMA-PET tumor characteristics.

Median age (range)	**72 years (49 – 88 years)**
Median PSA (range)	11.4 (1.1 – 920)
Gleason Score (biopsy)	
n/a	27 (20%)
≤ 6	24 (18%)
7a	6 (4%)
7b	7 (5%)
8	48 (36%)
9	19 (14%)
10	4 (3%)
Clinical T stage	
n/a	41 (30%)
1	57 (42%)
2	25 (19%)
3	9 (7%)
4	3 (2%)
D'Amico risk group	
n/a	22 (16%)
Low-risk	8 (6%)
Intermediate-risk	19 (14%)
High-risk	86 (64%)
Gleason Score (surgery)	
≤ 6	1 (3%)
7a	9 (27.5%)
7b	11 (33.5%)
8	4 (12%)
9	7 (21%)
10	1 (3%)
Median PSMA-TV (range)	3.8 ml (0 – 99.8 ml)
Median SUV_{max} (range)	11.0 (2.7 – 146.0)
Median SUV_{mean} (range)	6.4 (2.5 – 91.6)
Median ASP (range)	9.8 (0 – 149.7)

DISCUSSION

PSMA PET has shown great potential for focal treatment strategies. Bettermann and colleagues were able to show that PSMA PET-based tumor delineation is superior to MRI regarding the sensitivity to detect prostate cancer foci on whole mount histopathology specimens (21). Several studies are currently investigating focal treatment escalation by the implementation of PET imaging. Identification of the optimal imaging parameter as a surrogate for tumor aggressiveness is therefore an important need.

In this study, we examined the correlation between PET parameters and clinical risk factors in non-metastatic primary prostate cancer patients. We were able to validate prior publications that reported a moderate correlation between clinical risk parameters like Gleason score, PSA levels or D'Amico risk category and SUV_{max} of primary prostate tumors. Further analysis of additional quantitative PET parameters like ASP or PSMA-TV did not show superiority compared to SUV_{max} in this monocenter investigation. Only a moderate correlation of any investigated parameter with Gleason scores could be observed.

TABLE 2 | Correlation between initial PSA values and biopsy-derived Gleason scores with quantitative PSMA-PET parameters.

	PSMA-TV	**SUV_{max}**	**SUV_{mean}**	**ASP**
PSA	r = 0.366	r = 0.450	r = 0.442	r = 0.188
	p < 0.001	p < 0.001	p < 0.001	p = 0.031
	(n = 132)	(n = 131)	(n = 131)	(n = 132)
Gleason	r = 0.306	r = 0.307	r = 0.233	r = 0.171
	p = 0.001	p = 0.001	p = 0.016	p = 0.076
	(n = 108)	(n = 107)	(n = 107)	(n = 108)

The reported correlation coefficients in our study are comparable with published data on correlations between SUV_{max} and Gleason scores that ranged between 0.096 and 0.5 and correlation coefficients between SUV_{max} and PSA values that ranged between 0.071 and 0.57 (2, 10, 11, 22–27). All but one of these studies reported lower numbers of patients, **Supplementary Table 3** gives an overview of the published data on correlation coefficients.

Gleason scores of needle biopsies show discrepancies with surgical Gleason scores in up to 50% of cases, especially upgrading to higher Gleason scores is a frequent observation (28, 29). This can influence the observed correlations with quantitative PSMA metrics, probably underestimating the real Gleason score. Analysis of the patient sub-group that underwent surgery did not show any significant correlation between the investigated quantitative PET metrics and surgical Gleason grades. However, this is most likely due to the comparatively low number of patients in this sub-group, because correlation coefficients were similar to the correlation coefficients for biopsy-based Gleason scores.

Data on the correlation between quantitative PSMA PET metrics other than SUV_{max} and clinical risk factors are sparse. Meißner and colleagues reported a strong correlation between ASP and Gleason scores (rho 0.88) and a moderate correlation between tumor volume and Gleason scores (rho 0.51) in a small cohort of 37 patients (16). However, patients with lymphatic or distant metastases were not excluded in their analysis, the exact number of patients with extraprostatic lesions was unfortunately not reported. Hoberück et al. evaluated various quantitative PSMA PET metrics including SUV_{max}, SUV_{mean} and PSMA-TV. In a small cohort of 21 patients with consecutive PSMA scans before and during androgen deprivation therapy, they observed a strong correlation between the investigated PET parameters and no superiority of a specific parameter (30). The same quantitative parameters were investigated by Schmidkonz et al. in patients with bone metastases. They reported that all quantitative metrics were higher for Gleason scores > 7, but did not provide further comparative details (31).

Our study has several limitations. First, the retrospective nature of the investigation with its known limitations. Second, no spatial correlation analyses with whole-mount histology was performed in surgically resected patients. Current analyses in this regard showed an excellent correlation of PET parameters with intraprostatic tumor foci (32, 33). Third, the used radiotracer might not be the best modality for local tumor assessment. The high urinary clearance of [^{68}Ga]Ga-PSMA-11 hampers automatic delineation in close vicinity to the bladder. The necessary manual modifications are observer-dependent and might complicate independent reproducibility. Furthermore, high bladder uptake can potentially affect quantitative PET

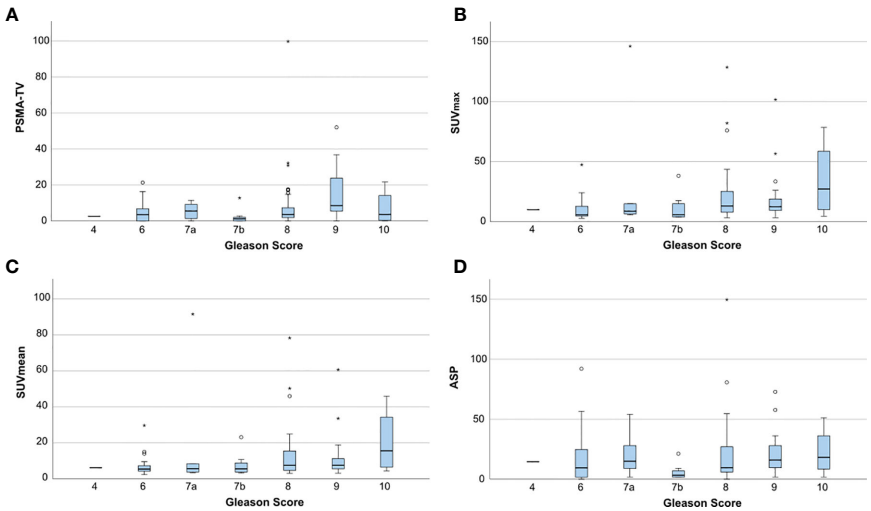

FIGURE 3 | Boxplots showing the distribution of quantitative PET parameters for each Gleason score. **(A)** PSMA-derived tumor volume (PSMA-TV), **(B)** Maximum standardized uptake value (SUVmax), **(C)** Mean standardized uptake value (SUVmean) and **(D)** Tumor asphericity (ASP). Outliers are plotted as points (< 3 * interquartile range) or asterisks (> 3 * interquartile range).

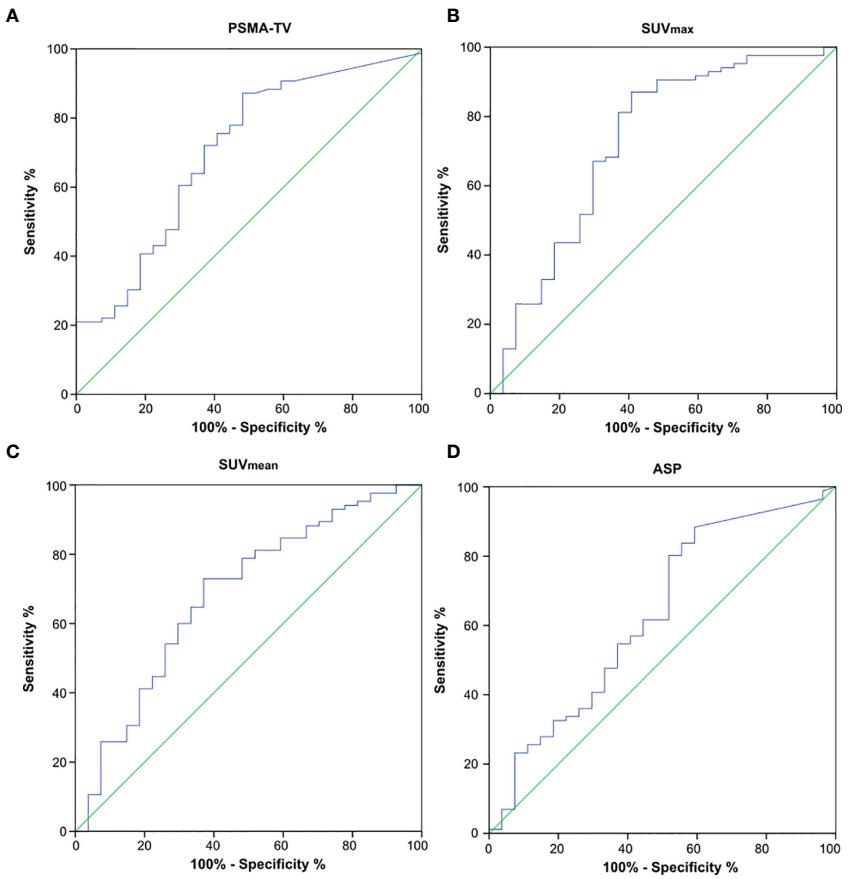

FIGURE 4 | Receiver operating characteristics (ROC) curves to detect high-risk prostate cancer using quantitative PSMA-PET parameters. **(A)** PSMA-derived tumor volume (PSMA-TV), **(B)** Maximum standardized uptake value (SUVmax), **(C)** Mean standardized uptake value (SUVmean) and **(D)** Tumor asphericity (ASP).

TABLE 3 | Area under the curve (AUC) characteristics for the investigated quantitative PSMA-PET parameters to detect high-risk prostate cancer.

	AUC	95% confidence interval
PSMA-TV	0.70	0.61 – 0.79
SUV_{max}	0.73	0.63 – 0.81
SUV_{mean}	0.68	0.59 - 0.77
ASP	0.63	0.53 - 0.72

TABLE 4 | Comparison of AUC characteristics to detect high-risk prostate cancer using the DeLong test.

	PSMA-TV	SUV_{max}	SUV_{mean}	ASP
PSMA-TV	–	difference: 0.023 p = 0.74	difference: 0.020 p = 0.80	difference: 0.073 p = 0.051
SUV_{max}	–	–	difference: 0.043 p = 0.035	difference: 0.096 p = 0.22
SUV_{mean}	–	–	–	difference: 0.053 p = 0.54

metrics of the prostate, e.g. by halo artifacts (34). The F-18-labeled PSMA-1007 radiotracer might be superior for evaluation of primary prostate cancer due to its favorable biodistribution, in particular lower bladder activity (35). Furthermore, SUV_{max} in primary prostate cancer lesions are systematically higher with [18F]F-PSMA-1007 compared to [68Ga]Ga-PSMA-11 (36). Nonetheless, a current meta-analysis was not able to show clear superiority of one of the specific PSMA radioligands in the recurrent situation (37). If prolonged uptake times are encountered in routine clinical care, [18F]F-PSMA-1007 could be advantageous over [68Ga]Ga-PSMA-11 by providing beneficial count statistics due to its longer physical half-life. Additionally, the higher positron range of Gallium-68 compared to Fluor-18 results in decreased spatial resolution, although Soderlund et al. observed only marginal differences using clinical PET scanners (38). The range of uptake times in the current analysis was relatively high, which might hamper inter-patient comparability of SUV. Lesion uptake of [68Ga]Ga-PSMA-11 increases over time after injection and has been described as approximately irreversible (39). However, the average increase in lesion SUV between 1h and 3h post injection has been reported to be moderate (25%) (40). The same PET scanner was used in all patients, which benefits comparability of PET parameters between patients. However, strictly speaking, applicability to other scanner models with different image properties and reconstruction methods would require dedicated analyses.

An important strength of our analysis is the restriction to patients without evidence of metastases by imaging including PSMA PET. Inclusion of metastatic patients might partly explain the high heterogeneity between previous publications, especially regarding correlation coefficients with PSA values (which is highly correlated with the total tumor volume). Additionally image evaluation was performed in a standardized fashion and with the observer being blinded to clinical risk parameters.

Overall, the observed association of the investigated quantitative imaging parameters with clinical risk factors is only fair. Novel methods like radiomics might be more suitable to detect high-risk sub-volumes within the prostate (41, 42).

In summary, this comprehensive analysis of quantitative PSMA PET metrics confirms prior studies that showed a moderate correlation with clinical risk factors. All investigated quantitative PET metrics intercorrelated and showed similar association with Gleason score, PSA values or D'Amico risk groups. The widely used reporting of SUV_{max} only seems therefore reasonable for personalized treatment options like focal boost in primary prostate cancer. Further prospective studies in a large cohort are needed to confirm our results, especially regarding the outcome after PET-guided personalized treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkomission der Charité Universitätsmedizin Berlin, Germany. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

Study conception and design: SZ and KH. Drafting of manuscript: SZ and SA. Image processing and analysis: SZ, FH, and JR. Study Investigators: SZ, SA, HA, CF, JR, MB, FH, and KH. Interpretation of data: all authors. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.879089/full#supplementary-material

REFERENCES

1. Petersen LJ, Zacho HD. PSMA PET for Primary Lymph Node Staging of Intermediate and High-Risk Prostate Cancer: An Expedited Systematic Review. *Cancer Imaging* (2020) 20:10. doi: 10.1186/s40644-020-0290-9
2. Cytawa W, Seitz AK, Kircher S, Fukushima K, Tran-Gia J, Schirbel A, et al. 68Ga-PSMA I&T PET/CT for Primary Staging of Prostate Cancer. *Eur J Nucl Med Mol Imaging* (2020) 47:168–77. doi: 10.1007/s00259-019-04524-z
3. Ambrosini V, Campana D, Polverari G, Peterle C, Diodato S, Ricci C, et al. Prognostic Value of 68Ga-DOTANOC PET/CT SUVmax in Patients With

Neuroendocrine Tumors of the Pancreas. *J Nucl Med* (2015) 56:1843–8. doi: 10.2967/jnumed.115.162719
4. Huang K, Schatka I, Rogasch JMM, Lindquist RL, De Santis M, Erber B, et al. Explorative Analysis of a Score Predicting the Therapy Response of Patients With Metastatic, Castration Resistant Prostate Cancer Undergoing Radioligand Therapy With 177Lu-Labeled Prostate-Specific Membrane Antigen. *Ann Nucl Med* (2021) 35:314–20. doi: 10.1007/s12149-020-01567-3
5. Komek H, Can C, Yilmaz U, Altindag S. Prognostic Value of 68 Ga PSMA I&T PET/CT SUV Parameters on Survival Outcome in Advanced Prostat Cancer. *Ann Nucl Med* (2018) 32:542–52. doi: 10.1007/s12149-018-1277-5
6. Vlachostergios PJ, Niaz MJ, Sun M, Mosallaie SA, Thomas C, Christos PJ, et al. Prostate-Specific Membrane Antigen Uptake and Survival in Metastatic Castration-Resistant Prostate Cancer. *Front Oncol* (2021) 11:630589. doi: 10.3389/fonc.2021.630589
7. Kerkmeijer LGW, Groen VH, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. *J Clin Oncol* (2021) 39:787–96. doi: 10.1200/JCO.20.02873
8. Nicholls L, Suh Y-E, Chapman E, Henderson D, Jones C, Morrison K, et al. Stereotactic Radiotherapy With Focal Boost for Intermediate and High-Risk Prostate Cancer: Initial Results of the SPARC Trial. *Clin Transl Radiat Oncol* (2020) 25:88–93. doi: 10.1016/j.ctro.2020.10.004
9. Zamboglou C, Spohn SKB, Adebahr S, Huber M, Kirste S, Sprave T, et al. PSMA-PET/MRI-Based Focal Dose Escalation in Patients With Primary Prostate Cancer Treated With Stereotactic Body Radiation Therapy (HypoFocal-SBRT): Study Protocol of a Randomized, Multicentric Phase III Trial. *Cancers (Basel)* (2021) 13:5795. doi: 10.3390/cancers13225795
10. Hong J-J, Liu B, Wang Z-Q, Tang K, Ji X-W, Yin W-W, et al. The Value of 18F-PSMA-1007 PET/CT in Identifying Non-Metastatic High-Risk Prostate Cancer. *EJNMMI Res* (2020) 10:138. doi: 10.1186/s13550-020-00730-1
11. Demirci E, Kabasakal L, Şahin OE, Akgün E, Gültekin MH, Doğanca T, et al. Can SUVmax Values of Ga-68-PSMA PET/CT Scan Predict the Clinically Significant Prostate Cancer? *Nucl Med Commun* (2019) 40:86–91. doi: 10.1097/MNM.0000000000000942
12. Apostolova I, Steffen IG, Wedel F, Lougovski A, Marnitz S, Derlin T, et al. Asphericity of Pretherapeutic Tumour FDG Uptake Provides Independent Prognostic Value in Head-and-Neck Cancer. *Eur Radiol* (2014) 24:2077–87. doi: 10.1007/s00330-014-3269-8
13. Hofheinz F, Lougovski A, Zöphel K, Hentschel M, Steffen IG, Apostolova I, et al. Increased Evidence for the Prognostic Value of Primary Tumor Asphericity in Pretherapeutic FDG PET for Risk Stratification in Patients With Head and Neck Cancer. *Eur J Nucl Med Mol Imaging* (2015) 42:429–37. doi: 10.1007/s00259-014-2953-x
14. Zschaeck S, Li Y, Lin Q, Beck M, Amthauer H, Bauersachs L, et al. Prognostic Value of Baseline [18F]-Fluorodeoxyglucose Positron Emission Tomography Parameters MTV, TLG and Asphericity in an International Multicenter Cohort of Nasopharyngeal Carcinoma Patients. *PloS One* (2020) 15: e0236841. doi: 10.1371/journal.pone.0236841
15. Wetz C, Rogasch J, Genseke P, Schatka I, Furth C, Kreissl M, et al. Asphericity of Somatostatin Receptor Expression in Neuroendocrine Tumors: An Innovative Predictor of Outcome in Everolimus Treatment? *Diagnostic (Basel)* (2020) 10:E732. doi: 10.3390/diagnostics10090732
16. Meißner S, Janssen J-C, Prasad V, Brenner W, Diederichs G, Hamm B, et al. Potential of Asphericity as a Novel Diagnostic Parameter in the Evaluation of Patients With 68Ga-PSMA-HBED-CC PET-Positive Prostate Cancer Lesions. *EJNMMI Res* (2017) 7:85. doi: 10.1186/s13550-017-0333-9
17. Rogasch JM, Cash H, Zschaeck S, Elezkurtaj S, Brenner W, Hamm B, et al. Ga-68-PSMA PET/CT in Treatment-Naïve Patients With Prostate Cancer: Which Clinical Parameters and Risk Stratification Systems Best Predict PSMA-Positive Metastases? *Prostate* (2018) 78(14):1103–10. doi: 10.1002/pros.23685
18. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol* (2016) 40:244–52. doi: 10.1097/PAS.0000000000000530
19. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer. *JAMA* (1998) 280:969–74. doi: 10.1001/jama.280.11.969
20. Draulans C, De Roover R, van der Heide UA, Kerkmeijer L, Smeenk RJ, Pos F, et al. Optimal 68ga-PSMA and 18F-PSMA PET Window Levelling for Gross Tumour Volume Delineation in Primary Prostate Cancer. *Eur J Nucl Med Mol Imaging* (2021) 48:1211–8. doi: 10.1007/s00259-020-05059-4
21. Bettermann AS, Zamboglou C, Kiefer S, Jilg CA, Spohn S, Kranz-Rudolph J, et al. [68ga-]PSMA-11 PET/CT and Multiparametric MRI for Gross Tumor Volume Delineation in a Slice by Slice Analysis With Whole Mount Histopathology as a Reference Standard - Implications for Focal Radiotherapy Planning in Primary Prostate Cancer. *Radiother Oncol* (2019) 141:214–9. doi: 10.1016/j.radonc.2019.07.005
22. Uprimny C, Kroiss AS, Decristoforo C, Fritz J, von Guggenberg E, Kendler D, et al. 68Ga-PSMA-11 PET/CT in Primary Staging of Prostate Cancer: PSA and Gleason Score Predict the Intensity of Tracer Accumulation in the Primary Tumour. *Eur J Nucl Med Mol Imaging* (2017) 44:941–9. doi: 10.1007/s00259-017-3631-6
23. Liu C, Liu T, Zhang N, Liu Y, Li N, Du P, et al. 68Ga-PSMA-617 PET/CT: A Promising New Technique for Predicting Risk Stratification and Metastatic Risk of Prostate Cancer Patients. *Eur J Nucl Med Mol Imaging* (2018) 45:1852–61. doi: 10.1007/s00259-018-4037-9
24. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous (68)Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. *Eur Urol* (2016) 70:829–36. doi: 10.1016/j.eururo.2015.12.053
25. Jena A, Taneja R, Taneja S, Singh A, Kumar V, Agarwal A, et al. Improving Diagnosis of Primary Prostate Cancer With Combined 68ga-Prostate-Specific Membrane Antigen-HBED-CC Simultaneous PET and Multiparametric MRI and Clinical Parameters. *AJR Am J Roentgenol* (2018) 211:1246–53. doi: 10.2214/AJR.18.19585
26. Sachpekidis C, Kopka K, Eder M, Hadaschik BA, Freitag MT, Pan L, et al. 68Ga-PSMA-11 Dynamic PET/CT Imaging in Primary Prostate Cancer. *Clin Nucl Med* (2016) 41:e473–9. doi: 10.1097/RLU.0000000000001349
27. Donato P, Roberts MJ, Morton A, Kyle S, Coughlin G, Esler R, et al. Improved Specificity With 68Ga PSMA PET/CT to Detect Clinically Significant Lesions "Invisible" on Multiparametric MRI of the Prostate: A Single Institution Comparative Analysis With Radical Prostatectomy Histology. *Eur J Nucl Med Mol Imaging* (2019) 46:20–30. doi: 10.1007/s00259-018-4160-7
28. Kvåle R, Møller B, Wahlqvist R, Fosså SD, Berner A, Busch C, et al. Concordance Between Gleason Scores of Needle Biopsies and Radical Prostatectomy Specimens: A Population-Based Study. *BJU Int* (2009) 103:1647–54. doi: 10.1111/j.1464-410X.2008.08255.x
29. Mian BM, Lehr DJ, Moore CK, Fisher HAG, Kaufman RP, Ross JS, et al. Role of Prostate Biopsy Schemes in Accurate Prediction of Gleason Scores. *Urology* (2006) 67:379–83. doi: 10.1016/j.urology.2005.08.018
30. Hoberück S, Löck S, Winzer R, Zöphel K, Froehner M, Fedders D, et al. [68ga] Ga-PSMA-11 PET Before and After Initial Long-Term Androgen Deprivation in Patients With Newly Diagnosed Prostate Cancer: A Retrospective Single-Center Study. *EJNMMI Res* (2020) 10:135. doi: 10.1186/s13550-020-00723-0
31. Schmidkonz C, Cordes M, Goetz TI, Prante O, Kuwert T, Ritt P, et al. 68Ga-PSMA-11 PET/CT Derived Quantitative Volumetric Tumor Parameters for Classification and Evaluation of Therapeutic Response of Bone Metastases in Prostate Cancer Patients. *Ann Nucl Med* (2019) 33:766–75. doi: 10.1007/s12149-019-01387-0
32. Zamboglou C, Kramer M, Kiefer S, Bronsert P, Ceci L, Sigle A, et al. The Impact of the Co-Registration Technique and Analysis Methodology in Comparison Studies Between Advanced Imaging Modalities and Whole-Mount-Histology Reference in Primary Prostate Cancer. *Sci Rep* (2021) 11:5836. doi: 10.1038/s41598-021-85028-5
33. Spohn SKB, Kramer M, Kiefer S, Bronsert P, Sigle A, Schultze-Seemann W, et al. Comparison of Manual and Semi-Automatic [18f]PSMA-1007 PET Based Contouring Techniques for Intraprostatic Tumor Delineation in Patients With Primary Prostate Cancer and Validation With Histopathology as Standard of Reference. *Front Oncol* (2020) 10:600690. doi: 10.3389/fonc.2020.600690
34. Heußer T, Mann P, Rank CM, Schäfer M, Dimitrakopoulou-Strauss A, Schlemmer H-P, et al. Investigation of the Halo-Artifact in 68Ga-PSMA-11-PET/MRI. *PloS One* (2017) 12:e0183329. doi: 10.1371/journal.pone.0183329

35. Giesel FL, Hadaschik B, Cardinale J, Radtke J, Vinsensia M, Lehnert W, et al. F-18 Labelled PSMA-1007: Biodistribution, Radiation Dosimetry and Histopathological Validation of Tumor Lesions in Prostate Cancer Patients. *Eur J Nucl Med Mol Imaging* (2017) 44:678–88. doi: 10.1007/s00259-016-3573-4
36. Kuten J, Fahoum I, Savin Z, Shamni O, Gitstein G, Hershkovitz D, et al. Head-To-Head Comparison of 68Ga-PSMA-11 With 18F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. *J Nucl Med* (2020) 61:527–32. doi: 10.2967/jnumed.119.234187
37. Alberts IL, Seide SE, Mingels C, Bohn KP, Shi K, Zacho HD, et al. Comparing the Diagnostic Performance of Radiotracers in Recurrent Prostate Cancer: A Systematic Review and Network Meta-Analysis. *Eur J Nucl Med Mol Imaging* (2021) 48:2978–89. doi: 10.1007/s00259-021-05210-9
38. Soderlund AT, Chaal J, Tjio G, Totman JJ, Conti M, Townsend DW. Beyond 18f-FDG: Characterization of PET/CT and PET/MR Scanners for a Comprehensive Set of Positron Emitters of Growing Application–18F, 11C, 89Zr, 124I, 68Ga, and 90Y. *J Nucl Med* (2015) 56:1285–91. doi: 10.2967/jnumed.115.156711
39. Ringheim A, Campos Neto G de C, Anazodo U, Cui L, da Cunha ML, Vitor T, et al. Kinetic Modeling of 68Ga-PSMA-11 and Validation of Simplified Methods for Quantification in Primary Prostate Cancer Patients. *EJNMMI Res* (2020) 10:12. doi: 10.1186/s13550-020-0594-6
40. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET Imaging With a [68Ga]Gallium-Labelled PSMA Ligand for the Diagnosis of Prostate Cancer: Biodistribution in Humans and First Evaluation of Tumour Lesions. *Eur J Nucl Med Mol Imaging* (2013) 40:486–95. doi: 10.1007/s00259-012-2298-2
41. Zamboglou C, Carles M, Fechter T, Kiefer S, Reichel K, Fassbender TF, et al. Radiomic Features From PSMA PET for Non-Invasive Intraprostatic Tumor Discrimination and Characterization in Patients With Intermediate- and High-Risk Prostate Cancer - A Comparison Study With Histology Reference. *Theranostics* (2019) 9:2595–605. doi: 10.7150/thno.32376
42. Spohn SKB, Bettermann AS, Bamberg F, Benndorf M, Mix M, Nicolay NH, et al. Radiomics in Prostate Cancer Imaging for a Personalized Treatment Approach - Current Aspects of Methodology and a Systematic Review on Validated Studies. *Theranostics* (2021) 11:8027–42. doi: 10.7150/thno.61207

Conflict of Interest: HA declares research grants, travel grants, and lecture fees from Sirtex Medical Europe; HA confirms that none of the above funding sources were involved in the preparation of this paper.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 28 April 2022
doi: 10.3389/fonc.2022.879310

Short-Term Outcomes and Clinical Efficacy of Stereotactic Body Radiation Therapy (SBRT) for Oligometastases of Prostate Cancer in China

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Edited by:
Constantinos Zamboglou, University of Freiburg Medical Center, Germany

Reviewed by:
Benjamin Maughan, University of Utah, United States
Francolini Giulio, University of Florence, Italy

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: 19 February 2022
Accepted: 28 March 2022
Published: 28 April 2022

Citation:
Xu C, Zhao X, Ju X, Shen Y, Qu M, Ye Y, Wang X, Yu C, Gao X and Zhang H (2022) Short-Term Outcomes and Clinical Efficacy of Stereotactic Body Radiation Therapy (SBRT) for Oligometastases of Prostate Cancer in China. Front. Oncol. 12:879310. doi: 10.3389/fonc.2022.879310

Objective: To assess the efficacy and safety of stereotactic body radiation therapy (SBRT) in managing oligometastases of prostate cancer. Moreover, it is the largest-to-date study in China to report the safety and efficacy of SBRT by CyberKnife for oligometastases of prostate cancer.

Methods: In this retrospective study, 75 patients with 108 oligometastases were treated by SBRT from May 2012 to February 2021. Among these patients, 43 patients were treated with the intention to control all known metastatic lesions and 32 were treated for palliative care. Patients received regular follow-up evaluations every 3 months. Efficacy was assessed based on local control (LC) rates, biochemical progression-free survival (bPFS), progression-free survival (PFS), and overall survival (OS). Safety was assessed based on clinical adverse events.

Results: Median follow-up time was 23.2 months (1.2-106.9 months). The complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) rates were 63.0%, 10.2%, 21.3% and 5.6%, respectively. The 6-month, 1-, and 2-year LC rates were 100%, 97.5%, and 96.0% respectively while the 6-month, 1-, and 2-year bPFS rates were 74.6%, 53.3%, and 47.9%, respectively. Additionally, 6-month, 1-, and 2-year PFS rates were 77.5%, 50.8%, and 47.2%, respectively. The 6-month, 1-, and 2-year OS rates were 97.0%, 88.8%, and 87.0%, respectively. For the 15 metastatic castration-resistant prostate cancer (mCRPC) patients with 23 lesions, the 2-year LC rates were 93.8%, while for 60 metastatic hormone-sensitive prostate cancer (mHSPC) patients with 85 lesions, the 2-year LC rates were 96.7%. No predictors of LC were found after univariate analysis. In those not on androgen deprivation therapy (ADT; n = 27), the 2-year freedom from ADT was 44.0%. All of the 24 patients with oligmetastase-induced complications experienced varying degrees of alleviation after SBRT. The treatment was well tolerated. No grade 3 or higher toxicity was observed.

Conclusion: SBRT is a safe and effective treatment modality in the management of oligometastases of mHSPC and mCRPC with high LC rates and acceptable toxicity. SBRT could provide a treatment choice for mCRPC, as well as an alternative to delay the start of ADT for mHSPC.

Keywords: oligometastases, stereotactic body radiotherapy (SBRT), metastatic castration-resistant prostate cancer (mCRPC), metastatic hormone-sensitive prostate cancer (mHSPC), efficacy

INTRODUCTION

Prostate cancer (PCa) is one of the most common genitourinary malignancies worldwide. The incidence and mortality of PCa has been increasing in China in the past decades. Metastatic PCa occurred in one-third of the patients after primary treatment (1). Systemic treatment for metastatic PCa was necessary, especially in patients with intermediate and high-risk of progression. Management options included androgen deprivation therapy (ADT), abiraterone, chemotherapy, immunotherapy, etc. (2, 3). Metastases-directed treatment included salvage surgery, external-beam radiotherapy, and brachytherapy, which may facilitate local control of metastatic lesions, relieve symptoms, and delay systemic treatment (4). However, the results have not been satisfactory including failure of tumor control, adverse reactions, and castration resistance. Therefore, exploration of more effective treatment to prolong tumor control and minimize toxicity is a much discussed topic.

Oligometastatic PCa is commonly proposed as an interim state between localized PCa and widely-spread PCa. In recent years, stereotactic body radiation therapy (SBRT) has emerged as one of the promising metastases-directed treatment options for oligometastatic malignancies. SBRT can be performed with a conventional linear accelerator or CyberKnife. Compared with conventional linear accelerator, CyberKnife has a real-time tracking system that can correct the beam angle by identifying the patient's breathing patterns, which is a huge innovation (5).

Several randomized phase 1/2 trials suggested the safety and potential benefits of SBRT for oligometastatic PCa. Compared with active surveillance, SBRT could prolong ADT-free survival (21 months vs 13 months). Quality of life (QoL) was similar between the two groups and no grade 2-5 toxicity was reported in a median follow-up time of 3 years (6). One recent phase 2 trial compared progression at 6 months between SBRT and observation in 54 metastatic PCa patients after randomization in a 2:1 ratio. Progression (defined as prostate-specific antigen level increase, progression detected by conventional imaging, symptomatic progression, ADT initiation for any reason, or death) rate at 6 months were 19% vs 61% (P=0.005) between the two groups. These studies provided preliminary evidence for application of SBRT in metastatic PCa (7). However, limitations of these studies include relatively small sample size and lack of long-term follow-up results.

Thus, the role of SBRT as a metastases-directed therapy for oligometastases remained to be explored. The aim of this real-world analysis was to assess the efficacy and safety of SBRT by CyberKnife for oligometastatic PCa.

Abbreviations: SBRT, Stereotactic body radiation therapy; LC, local control; bPFS, Biochemical progression free survival; PFS, Progression free survival; OS, Overall survival; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; mCRPC, Metastatic castration-resistant prostate cancer; mHSPC, Metastatic hormone-sensitive prostate cancer; ADT, Androgen deprivation therapy; QoL, Quality of life; PCa, Prostate cancer; CT, Computed tomography; GTV, Gross tumor volume; PTV, Planning target volume; AE, Adverse events; PSA, Prostate-specific antigen; PSMA, Prostate-specific membrane antigen; CTCAE, Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors.

MATERIAL AND METHODS

Participants

We reviewed all the oligometastatic PCa patients treated with SBRT at any line at First Affiliated Hospital of Navy Medical University. All these patients were examined by an oncologist to confirm the diagnosis of metastatic PCa before the treatment. Patients with oligmetastases (no more than 5) diagnosed by imaging examinations (e.g. MR, Bone scan, FDG PET/CT, PSMA PET/CT, or PSMA PET/MR), a Karnofsky performance score no less than 70, a life expectancy of over 3 months were included in the study. Patients who declined SBRT or were unsuitable for SBRT due to comorbidities were excluded. Patients were also excluded if the metastatic lesion had been previously treated by radiotherapy. Informed consents were obtained from all patients prior to the enrollment and the study was conducted according to the Declaration of Helsinki. The study protocol was reviewed and approved by the Medical Ethics Committee of First Affiliated Hospital of Navy Medical University. In total, 75 patients with oligometastases of PCa (total 108 lesions) between May 2012 and February 2021 constituted the dataset.

Treatments

Of the 75 patients, 43 were treated with the intent to control all known metastatic lesions, and 32 underwent SBRT for palliation of oligometastases. SBRT was delivered by CyberKnife (Accuray Corporation, Sunnyvale, CA, USA). Patients were immobilized in supine position with arms by their sides using thermoplastic body mask. Enhanced computed tomography (CT) scan was performed with a slice thickness of 1.5 **mm**, with the scan range of at least 10 **cm** below and above the tumor. The gross tumor volume (GTV) was defined as a radiographically lesion in the oligometastases. According to the metastases motion, planning target volume (PTV) was delineated with a 2-6 **mm** margin expansion in lateral direction and in anteroposterior direction respectively, a 2-8 **mm** margin expansion incephalo-caudal

direction from GTV. For 68 patients, X-sight spine tracking was used, while 4 patients with synchrony respiratory motion tracking and 3 patients with 6D-skull tracking. X-sight spine tracking was employed for SBRT in 68 patients with 101 lesions, while synchrony respiratory motion tracking was performed in 4 patients with 4 lesions and 6D-skull tracking in 3 patients with 3 lesions. The dose-volume constraints for organs at risk were referred to the American Association of Physicists in Medicine guidelines in TG-101 (8).

Outcome Measurements and Follow-Up

The primary outcome of efficacy was local control (LC) rate. Secondary outcomes include biochemical progression-free survival (bPFS), progression-free survival (PFS), overall survival (OS), and adverse events (AE). Serum prostate-specific antigen (PSA) and/or testosterone levels of the patients were checked every month. Biochemical failure was defined as (1) in the case of the initial decline from baseline after SBRT, the first PSA increase that was 25% and 2 ng/ml above the nadir, or an increase that was 25% and greater than the pre-treatment PSA value, as confirmed by a second value 3 or more weeks later; or (2) in the case of no initial decline from baseline, a PSA increase that was 25% and 2 ng/ml greater than baseline after 3 months if baseline PSA was 2 ng/ml, or PSA increase that was 25% after 3 months if baseline PSA was <2 ng/ml (9).

Contrast-enhanced CT scans, SPECT, 68-Ga Prostate-specific membrane antigen (PSMA) PET/CT scans, or contrast-enhanced MRI was performed every 3 months after radiotherapy to monitor recurrence or progression. Adverse events, amelioration of symptoms and sequential treatment were recorded. Acute and late toxicity were scored according to the Common Terminology Criteria for Adverse Events (CTCAE) version 6.0. LC was defined as complete response (CR), partial response (PR), and stable disease (SD). Tumor response was determined using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (10). OS was defined as the time from the start of SBRT to the death of any cause or the last follow-up. PFS was defined as the time from the start of SBRT to the confirmation of disease progressions at any site or death by any cause.

Statistical Analysis

The curves of LC, bPFS, PFS, and OS were calculated by the Kaplan-Meier method. Potential factors associated with LC rate were identified with univariate log-rank comparisons. Statistical analyses were performed using SPSS 18.0 (IBM Corporation, Armonk, NY, USA). Two-sided P values <0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Basic characteristics of the 75 patients were analyzed. The median age of study cohort was 68 years, ranging from 51 to 88 years. The median PSA at PCa diagnosis and before SBRT for oligometastases was 44.7 ng/m and 4.5 ng/ml, respectively. Nearly two-thirds of the patients (49/75) had primary tumor with Gleason score 8 or higher. Among the 108 metastases, 12.0% (13/108) were lymph node metastases (N1 or M1a), 82.4% (89/108) were bone metastases (M1b), and 5.6% (6/108) had visceral metastases (M1c). Twenty-three patients (30.7%) had more than one metastatic lesion. According to the CHAARTED criteria (11), 8.0% (6/75) of the patients had high metastatic burden. Median time duration between PCa diagnosis and oligometastases diagnosis was 30.1 months (range 11.6-45.8 months). While median time duration between oligometastases diagnosis and SBRT was 1.4 months (range 0.5-5.5 months). Detailed information of patient characteristics was is in **Table 1**. The treatment parameters are presented in **Table 2**.

Efficacy Outcomes

The median follow-up duration after SBRT was 23.2 months (range 1.2-106.9 months). The 6-month, 1-, 2-year LC rates were 100%, 97.5%, 96.0%, respectively (**Figure 1A**). Based on the RECIST criteria, the CR, PR, and SD rates were 63.0%, 10.2%, and 21.3% respectively, while six (5.6%) lesions of five patients had disease progression (PD) among the 108 metastatic lesions after SBRT. Detailed information is shown in **Table 3**. For detailed information of local progressive disease, see **Table S1**. For the 15 metastatic castration-resistant prostate cancer (mCRPC) patients with 23 lesions, the 2-year LC rate was 93.8% while for 60 metastatic hormone-sensitive prostate cancer (mHSPC) patients with 85 lesions, the 2-year LC rate was 96.7%. In the univariate analysis, mCRPC patients after SBRT had a similar LC rate with those mHSPC patients (P=0.898). Similarly, no other predictors was associated with LC after univariate analysis (**Table 4**). In those not on ADT (n= 27), the 2-year freedom from ADT was 44.0%. Among the patients who had olgmetastases-induced symptoms prior to the treatment (including 21 with corresponding pain and 3 with physical weakness), all of them (100.0%) had varying degrees of alleviations of symptoms after SBRT.

The 6-, 12- and 24-month bPFS was 74.6%, 53.3% and 47.9%, respectively (**Figure 1B**). The results of PFS were similar. The 6-, 12- and 24-month PFS was 77.5%, 50.8% and 47.2%, respectively (**Figure 1C**). Median time to distant progression was slightly longer than biochemical failure (25.1 month vs 24.9 month). Meanwhile, a total of 48 patients experienced distant progression. Most newly discovered metastases involved single organ such as bone, lymph node, and lung, which were treated with hormone therapy, chemotherapy, radiation therapy, or combination therapy.

At the last follow-up, 18 patients (24.0%) died while 57 were alive. One patient died of pneumonia and renal failure, respectively, whereas 16 patients died of distant metastasis. Hence, local failure and radiation-induced toxicity did not contribute to the deaths. The 6-month, 1-, 2-year OS was 97.0%, 88.8%, 87.0%, respectively (**Figure 1D**).

TABLE 1 | Patient characteristics.

Characteristics	All patients (N=75)
Age at SBRT-year	68 (range 51-88)
Karnofsky performance score ≥70	75 (100%)
PSA at primary diagnosis-ng/ml	44.7(3.4-999.9)
PSA before SBRT-ng/ml	4.5 (0.001-999.9)
Gleason Score	
6	1 (1.3%)
7	20 (26.7%)
8	16 (21.3%)
9	28 (37.3%)
10	5 (6.7%)
N/O	5 (6.7%)
No. of metastatic lesions at SBRT	
1	52 (69.3%)
2	16 (21.3%)
3	5 (6.7%)
4	1 (1.3%)
5	1 (1.3%)
Number of metastases	
Lymph node metastases	
Regional lymph nodes (N1)	6 (5.6%)
Non-regional lymph nodes (M1a)	7 (6.5%)
Bone metastases (M1b)	
Axial	60 (55.6%)
Appendicular	29 (26.9%)
Visceral metastases (M1c)	
Lung metastases	3 (2.8%)
Brain metastases	1 (0.9%)
Adrenal gland metastases	2 (1.9%)
Castration-sensitivity before SBRT	
mCRPC	15 (20%)
mHSPC with ADT	33 (44%)
mHSPC without ADT	27 (36%)
Diagnosis time of oligometastases	
Primary oligometastatic prostate cancer	29 (38.7%)
Relapse after radical surgery	35 (46.7%)
Relapse after radical RT	11 (14.7%)
Imaging modality at recurrence	
F-18 FDG PET/CT	21 (28.0%)
Ga-68 PSMA-PET/CT	23 (30.7%)
Ga-68 PSMA-PET/MR	11 (14.7%)
SPECT	11 (14.7%)
MR	9 (12.0%)
Time from primary diagnosis to metastases-month	12.8 (0.0-122.1)
Time from metastases to SBRT-month	1.6 (0.0-58.8)

SBRT, Stereotactic body radiation therapy; PSA, Prostate specific antigen; N/O, Not obtained; mCRPC, Metastatic castration-resistant prostate cancer; mHSPC, Metastatic hormone-sensitive prostate cancer; ADT, Androgen deprivation therapy; RT, radiation therapy; SPECT, Single-Photon Emission Computed Tomography.

Toxicity

TABLE 2 | Treatment parameters for SBRT.

Parameters	Median (Range)
GTV (ml)	7.8 (0.5-83.3)
Total prescribed dose (Gy)	33.6 (16 - 45)
Number of fractions	5 (4 - 8)
Dose per fraction (Gy)	6.5 (4 - 8)
$BED_{1.5}$ (Gy)	170.9 (58.7-270.0)
Maximum dose (Gy)	46.3 (23.3-69.7)
Prescription isodose line (%)	72 (61 – 89)

GTV, Gross tumor volume; $BED_{1.5}$, Biologic equivalent dose (α/β=1.5Gy).

SBRT was well-tolerated in PCa patients with oligometastases. No Grade 3 or higher adverse events were reported. Early toxicities after treatment included fatigue, nausea, decreased appetite, and leucopenia. Late complications included localized fibrosis, urinary frequency, etc. No fracture was observed during follow-up. All the early adverse effects were temporary, and cured by symptomatic medication.

DISCUSSION

This study evaluated the efficacy and safety of SBRT in oligometastatic PCa with lesions up to five. In a median follow-up duration of nearly 2 years, SBRT provided survival benefits with high LC rates. No severe adverse events (grade 3 or more) were reported.

Efficacy of SBRT in oligometastatic PCa has been evaluated in several studies. One prospective, single institutional clinical trial recruited 199 patients with relapsing oligometastatic PCa (lesions up to five) following definitive local treatment for primary PCa. After SBRT (50 Gy in 10 fractions) to each visible lesion, the median treatment escalation-free survival was 27.1 months, with 51.7% of the patients requiring no treatment escalation 2 years following SBRT (12). Apart from prolonging treatment escalation-free survival, SBRT may improve quality of life (QoL) because of a delay of more toxic salvage therapies (13). In a prospective clinical trial, stereotactic ablative body radiotherapy (SABR) for oligometastatic PCa in 22 patients not on ADT, the 2-yr freedom from ADT was 48.0% (14). Similarly, 27 patients were not on ADT in our study, and the 2-year freedom from ADT was 44.0%. In a large international study cohort of 1033 patients with extracranial oligometastases, SBRT provided favorable long-term OS and wide-spread progression rates, especially in the PCa patients (132 cases). The 3-year OS rate was 87.9% in the patients with PCa oligometastases (15), while 2-year OS rates were 87.0% in our study.

Another study included 64 oligorecurrent or oligoprogressive PCa (lesions up to five) and the median follow-up was 15.2 months. Rates of LC at 6-, 12- and 18-months were 94%, 88% and 84%. In the study cohort, CRPC patients had worse PFS compared with HSPC patients (16). However, in our study, mCRPC patients after SBRT had a similar LC rate as those with mHSPC (P=0.898). The 6-month, 1-, and 2-year LC rates were 100%, 97.5%, and 96.0%, respectively, which was higher than in the study mentioned above. It could be possible that combination use of SBRT and novel anti-androgen agents (e.g. Arbiraterone) led to this result for mCRPC patients (17). Ongoing trials are focusing on the combination of SBRT and other treatments in the scenario of oligometastatic CRPC (e.g., NCT02816983, NCT03503344, NCT03449719). The result of our study would contribute to this particular scientific interest, especially in the Chinese population.

Different metastatic patterns might not influence efficacy of SBRT. Bone and lymph node metastases were the most common in PCa patients. A multi-institutional study reported clinical data

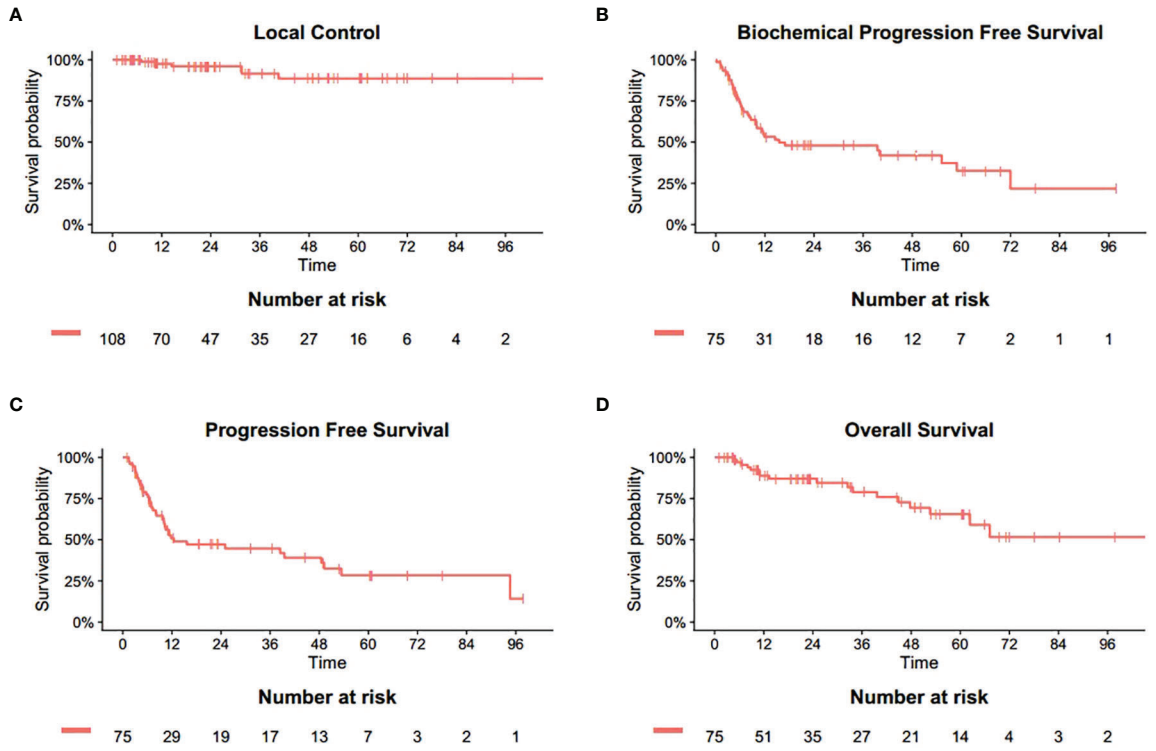

FIGURE 1 | Actuarial survival analysis of patients. **(A)** Overall local control. **(B)** Overall biochemical progression free survival. **(C)** Overall progression free survival. **(D)** Overall survival.

TABLE 3 | Local control following SBRT.

Metastatic sites	CR	PR	SD	PD
Lymph node (N=13)	10	–	3	–
Pelvic (N=6)	3	–	3	–
Extrapelvic (N=7)	7	–	–	–
Bone (N=89)	55	9	19	6
Axial (N=60)	36	6	13	5
Appendicular (N=29)	19	3	6	1
Visceral (N=6)	3	2	1	–
Lung (N=3)	2	1	–	–
Adrenal gland (N=2)	1	1	–	–
Brain (N=1)	–	–	1	–

CR, complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease.
For detailed information of progressive disease, see ***Table S1****.*

of 74 PCa patients with bone-only oligometastases (lesions up to 5). The 2-year PCa-specific survival (PCSS) and PFS rates were 92.0% and 72.0%, with LC rate of 95.4% per lesion. Single oligometastases and PSA response were associated with better PCSS and PFS in the multivariable analysis (18). A phase 2 trial evaluated high-dose SBRT for patients with lymph node oligometastases (lesions up to 3), most of whom were PCa patients. The OS at 1, 2, and 3 years were 97.3%, 94.2%, 84%, and PFS at 1, 2, and 3 years were 67.4%, 49.6%, and 46.1%. SBRT was well-tolerated among these patients (19). Another prospective phase 2 trial reported 5-year OS, PFS, and bPFS to be 96.9%, 88.2%, and 91.4% in 44 patients with locally advanced, node-positive, and bone oligometastatic PCa, using extreme hypofractioned radiation therapy (20). The similar results were observed in our study.

Combining other treatment modalities might improve the efficacy of SBRT. For instance, concurrent sunitinib and SBRT significantly improve the overall survival of PCa oligometastases (HR = 0.25, p = 0.04) (21). Combining cytoreductive prostatectomy and SBRT for bone metastases were evaluated in

TABLE 4 | Univariate analysis for LC rate.

	1-year LC rate (%)	2-year LC rate(%)	P Value
Castration-sensitivity			
mHSPC	98.4	96.7	0.898
mCRPC	93.8	93.8	
$BED_{1.5}$ (Gy)			
<180	96.5	94.4	0.104
≥180	100	100	
GTV(ml)			
<20	100	100	0.053
≥20	88.4	81.1	
Systemic therapy after SBRT			
Yes	97.0	95.3	0.300
No	100	100	

LC, local control; mCRPC, Metastatic castration-resistant prostate cancer; mHSPC, Metastatic hormone-sensitive prostate cancer; $BED_{1.5}$, Biologic equivalent dose (α/β=1.5Gy); GTV, Gross tumor volume; SBRT, Stereotactic body radiation therapy.

one retrospective cohort. Of the 58 patients, the 3-year CRPC-free survival and cancer-specific survival was 75.9% and 91.4% (22).

Toxicities of SBRT included bowel complications, bladder complications, and bone fractures in metastases-directed treatment (23). In this study, no grade 3 or more adverse events were reported. All the adverse events during follow-up were tolerable and controlled through medication. No bone fractures occurred.

Inevitably, this study has several limitations. First, selection bias could not be ruled out. The study cohort included both mHSPC and mCRPC patients, and most of the patients received one or more systemic treatments before or after SBRT. Second, a number of important values such as PSA levels in the follow up, primary tumor stage, and Gleason score of primary tumor were missing. This might lead to underestimation of the tumor aggressiveness and risk of progression. Third, PSMA-imaging, which was considered one of the most sensitive imaging modalities for detection and evaluation of metastatic lesions, has been applied only in recent years in our center. Although approximately half of these patients were diagnosed by PSMA-PET/CT or PSMA-PET/MR, still some patients were evaluated based on enhanced SPECT or MRI. Neglecting micro-metastases may possibly lead to distant progression after SBRT. Last but not least, this study was limited by its retrospective nature.

CONCLUSION

SBRT is an effective metastases-directed therapy for oligometastatic PCa with a high local control rate. Toxicity of SBRT could be well-tolerated. Distant metastases and biological progression still occurred after SBRT, implying the importance of systemic treatment in high-risk oligometastatic PCa patients. Still, prospective studies with long-term follow-up results were required to validate the efficacy and safety of SBRT for oligometastatic PCa patients in China.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Shanghai Changhai Hospital of the Navy Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CX and XZ conceived and designed the experiments and wrote the paper. XJ, YS, MQ, YY, and XW helped to collect and analyze the data. CY helped to analyze the treatment planning. XG and HZ revised the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This study is sponsored by the First Affiliated Hospital of Navy Medical University "234 Subject Climbing Program" (2019YPT004), the First Affiliated Hospital of Navy Medical University "Youth Startup Fund" (2020QNB10).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.879310/full#supplementary-material

REFERENCES

1. Siegel R, Miller K, Fuchs H, Jemal A. Cancer Statistics, 2022. *CA: Cancer J Clin* (2022) 72(1):7-33. doi: 10.3322/caac.21708
2. Connor M, Shah T, Horan G, Bevan C, Winkler M, Ahmed H. Cytoreductive Treatment Strategies for *De Novo* Metastatic Prostate Cancer. *Nat Rev Clin Oncol* (2020) 17(3):168–82. doi: 10.1038/s41571-019-0284-3
3. Sartor O, de Bono J. Metastatic Prostate Cancer. *N Engl J Med* (2018) 378 (7):645–57. doi: 10.1056/NEJMra1701695
4. Lecouvet F, Oprea-Lager D, Liu Y, Ost P, Bidaut L, Collette L, et al. Use of Modern Imaging Methods to Facilitate Trials of Metastasis-Directed Therapy for Oligometastatic Disease in Prostate Cancer: A Consensus Recommendation From the EORTC Imaging Group. *Lancet Oncol* (2018) 19(10):e534–e45. doi: 10.1016/S1470-2045(18)30571-0
5. Dieterich S, Gibbs I. The CyberKnife in Clinical Use: Current Roles, Future Expectations. *Front Radiat Ther Oncol* (2011) 43:181–94. doi: 10.1159/000322423
6. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol Off J Am Soc Clin Oncol* (2018) 36(5):446–53. doi: 10.1200/JCO.2017.75.4853
7. Phillips R, Shi W, Deek M, Radwan N, Lim S, Antonarakis E, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol* (2020) 6(5):650–9. doi: 10.1001/jamaoncol.2020.0147
8. Benedict S, Yenice K, Followill D, Galvin J, Hinson W, Kavanagh B, et al. Stereotactic Body Radiation Therapy: The Report of AAPM Task Group 101. *Med Physics* (2010) 37(8):4078–101. doi: 10.1118/1.3438081
9. Scher H, Halabi S, Tannock I, Morris M, Sternberg C, Carducci M, et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol Off J Am Soc Clin Oncol* (2008) 26(7):1148–59. doi: 10.1200/JCO.2007.12.4487
10. Bogaerts J, Ford R, Sargent D, Schwartz L, Rubinstein L, Lacombe D, et al. Individual Patient Data Analysis to Assess Modifications to the RECIST Criteria. *Eur J Cancer (Oxford Engl 1990)* (2009) 45(2):248–60. doi: 10.1016/j.ejca.2008.10.027
11. Kyriakopoulos C, Chen Y, Carducci M, Liu G, Jarrard D, Hahn N, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. *J Clin Oncol Off J Am Soc Clin Oncol* (2018) 36 (11):1080–7. doi: 10.1200/JCO.2017.75.3657
12. Bowden P, See A, Frydenberg M, Haxhimolla H, Costello A, Moon D, et al. Fractionated Stereotactic Body Radiotherapy for Up to Five Prostate Cancer Oligometastases: Interim Outcomes of a Prospective Clinical Trial. *Int J Cancer* (2020) 146(1):161–8. doi: 10.1002/ijc.32509
13. Azzam G, Lanciano R, Arrigo S, Lamond J, Ding W, Yang J, et al. SBRT: An Opportunity to Improve Quality of Life for Oligometastatic Prostate Cancer. *Front Oncol* (2015) 5:101. doi: 10.3389/fonc.2015.00101
14. Siva S, Bressel M, Murphy D, Shaw M, Chander S, Violet J, et al. Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial. *Eur Urol* (2018) 74(4):455–62. doi: 10.1016/j.eururo.2018.06.004
15. Poon I, Erler D, Dagan R, Redmond KJ, Foote M, Badellino S, et al. Evaluation of Definitive Stereotactic Body Radiotherapy and Outcomes in Adults With Extracranial Oligometastasis. *JAMA Netw Open* (2020) 3(11):e2026312. doi: 10.1001/jamanetworkopen.2020.26312
16. Franzese C, Zucali P, Di Brina L, D'Agostino G, Navarria P, Franceschini D, et al. The Efficacy of Stereotactic Body Radiation Therapy and the Impact of Systemic Treatments in Oligometastatic Patients From Prostate Cancer. *Cancer Med* (2018) 7(9):4379–86. doi: 10.1002/cam4.1707
17. Detti B, D'Angelillo R, Ingrosso G, Olmetto E, Francolini G, Triggiani L, et al. Combining Abiraterone and Radiotherapy in Prostate Cancer Patients Who Progressed During Abiraterone Therapy. *Anticancer Res* (2017) 37(7):3717–22. doi: 10.21873/anticanres.11744
18. Onal C, Ozyigit G, Akgun Z, Atalar B, Igdem S, Oymak E, et al. Oligometastatic Bone Disease in Castration-Sensitive Prostate Cancer Patients Treated With Stereotactic Body Radiotherapy Using 68ga-PSMA PET/CT: TROD 09-004 Study. *Clin Nucl Med* (2021) 46(6):465–70. doi: 10.1097/RLU.0000000000003558
19. Franzese C, Comito T, Tripoli A, Franceschini D, Clerici E, Navarria P, et al. Phase II Trial of High Dose Stereotactic Body Radiation Therapy for Lymph Node Oligometastases. *Clin Exp Metastasis* (2020) 37(5):565–73. doi: 10.1007/s10585-020-10047-x
20. Narang K, Kadian M, Venkatesan K, Mishra S, Bisht S, Gupta D, et al. Phase I/II Study of Extreme Hypofractionated Stereotactic Body Radiation Therapy Boost to Prostate for Locally Advanced, Node-Positive and Oligometastatic Cancer. *Cureus* (2020) 12(11):e11751. doi: 10.7759/cureus.11751
21. Kao J, Chen C, Tong C, Packer S, Schwartz M, Chen S, et al. Concurrent Sunitinib and Stereotactic Body Radiotherapy for Patients With Oligometastases: Final Report of a Prospective Clinical Trial. *Target Oncol* (2014) 9(2):145–53. doi: 10.1007/s11523-013-0280-y
22. Xue P, Wu Z, Wang K, Gao G, Zhuang M, Yan M. Oncological Outcome of Combining Cytoreductive Prostatectomy and Metastasis-Directed Radiotherapy in Patients With Prostate Cancer and Bone Oligometastases: A Retrospective Cohort Study. *Cancer Manage Res* (2020) 12:8867–73. doi: 10.2147/CMAR.S270882
23. De Bleser E, Jereczek-Fossa BA, Pasquier D, Zilli T, Van As N, Siva S, et al. Metastasis-Directed Therapy in Treating Nodal Oligorecurrent Prostate Cancer: A Multi-Institutional Analysis Comparing the Outcome and Toxicity of Stereotactic Body Radiotherapy and Elective Nodal Radiotherapy. *Eur Urol* (2019) 76(6):732–9. doi: 10.1016/j.eururo.2019.07.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 17 May 2022
doi: 10.3389/fonc.2022.862995

Oligoprogression in Metastatic, Castrate-Resistant Prostate Cancer—Prevalence and Current Clinical Practice

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OPEN ACCESS

Edited by:
Constantinos Zamboglou, University of Freiburg Medical Center, Germany

Reviewed by:
Giulia Marvaso, University of Milan, Italy
Stephanie Kroeze, University Hospital Zürich, Switzerland

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: 26 January 2022
Accepted: 01 April 2022
Published: 17 May 2022

Citation:
Patel PH, Tunariu N, Levine DS, de Bono JS, Eeles RA, Khoo V, Murray J, Parker CC, Pathmanathan A, Reid A, van As N and Tree AC (2022) Oligoprogression in Metastatic, Castrate-Resistant Prostate Cancer—Prevalence and Current Clinical Practice. Front. Oncol. 12:862995. doi: 10.3389/fonc.2022.862995

Aims: Oligoprogression is poorly defined in current literature. Little is known about the natural history and significance of oligoprogression in patients with hormone-resistant prostate cancer on abiraterone or enzalutamide treatment [termed androgen receptor-targeted therapy (ARTT)]. The aim of this study was to determine the prevalence of oligoprogression, describe the characteristics of oligoprogression in a cohort of patients from a single center, and identify the number of patients potentially treatable with stereotactic body radiotherapy (SBRT).

Methods: Castration-resistant prostate cancer (CRPC) patients who radiologically progressed while on ARTT were included. Patients with oligoprogressive disease (OPD) (≤3 lesions) on any imaging were identified in a retrospective analysis of electronic patient records. Kaplan–Meier method and log-rank test were used to calculate progression-free and overall survival.

Results: A total of 102 patients with metastatic CRPC on ARTT were included. Thirty (29%) patients presented with oligoprogression (46 lesions in total); 21 (21% of total) patients had lesions suitable for SBRT. The majority of lesions were in the bone (21, 46%) or lymph nodes (15, 33%). Patients with oligoprogression while on ARTT had a significantly better prostate-specific antigen (PSA) response on commencing ARTT as compared to patients who later developed polyprogression. However, PSA doubling time immediately prior to progression did not predict OPD. Median progression-free survival to oligoprogression versus polyprogression was 16.8 vs. 11.7 months. Time to further progression after oligoprogression was 13.6 months in those treated with radiotherapy (RT) for oligoprogression vs. 5.7 months in those treated with the continuation of ARTT alone.

Conclusions: In this study, nearly a third of patients on ARTT for CRPC were found to have OPD. OPD patients had a better PSA response on ART and a longer duration on ARTT before developing OPD as compared to those developing polyprogressive disease

(Poly-PD). The majority of patients (70%) with OPD had lesions suitable for SBRT treatment. Prospective randomized control trials are needed to establish if there is a survival benefit of SBRT in oligoprogressive prostate cancer and to determine predictive indicators.

Keywords: oligoprogression, stereotactic body radiotherapy, castrate resistant prostate cancer, abiraterone, enzalutamide, Androgen receptor targeted therapy, Oligoprogressive disease (OPD)

1 INTRODUCTION

Prostate cancer accounts for 26% of all new cancer cases in men, with up to 60% of cases diagnosed at a late stage in the United Kingdom (1). Castration-resistant prostate cancer (CRPC) describes a disease resistant to castration and is a life-limiting disease with a median survival of 25 months (2). Advances in treatment including the introduction of oral targeted therapies, which suppress the androgen receptor signaling pathway such as abiraterone and enzalutamide, have been proven in large, phase III randomized control trials to improve survival for CRPC patients (3–7). These androgen receptor-targeted therapies (ARTTs) give relatively minor toxicity as compared to systemic chemotherapy, maintaining quality of life and offering an additional line of treatment.

However, as with many systemic treatments, ARTT can lose efficacy over time. Patients typically develop resistant clones within 15–17 months (5, 7), with multiple mechanisms of resistance recognized (8).

Metastasis-directed therapy (MDT) for oligoprogressive disease (OPD) is a rapidly evolving potential treatment strategy. In some tumor sites, consensus guidelines have been created to characterize oligometastatic disease, but MDT for oligometastatic disease is not yet proven to improve overall survival (OS), although it has become an increasingly considered treatment option due to supporting phase II trial data (9–11). Phase III trial data are, however, awaited. OPD is still an emerging concept in prostate cancer with no prospective, randomized, phase II data on outcomes of these patients treated with or without MDT. OPD to an extent is defined by the imaging modality used, with whole-body diffusion-weighted MRI (WBDWMRI) and PET/CT being more sensitive at detecting bone progression than standard imaging (12).

OPD in broad terms includes patients with established metastatic disease with only a few lesions (usually considered as 3 or less) progressing on a background of all other metastatic sites remaining responsive to current systemic treatment (13). Patients therefore need to have shown an initial response prior to developing OPD. The hypothesis underlying treating OPD with MDT is to allow the systemic therapy to continue to work on the remaining sites, preserving the efficacy of the systemic therapy to the responsive lesions while eliminating macroscopic resistant clones with MDT. Within CRPC, this is particularly desirable when patients established on ARTT present with OPD. MDT to OPD may delay more toxic chemotherapy and improve progression-free survival (PFS) and OS. With the use of a well-tolerated treatment with a high local control rate such as stereotactic body radiotherapy (SBRT) (14–16), it is hypothesized that patient quality of life can be preserved as well. CRPC patients are often an older and frailer population in whom maintaining tolerated treatments for longer may have a significant impact on survival.

Currently, OPD is defined by the number of sites of the disease progressing. In the absence of biological hallmarks of OPD and characteristics determining prognosis, there is insufficient evidence to justify any further detailed definitions. This retrospective study aimed to quantify the prevalence of OPD in patients on ARTT and describe characteristics identified in patients with OPD on ARTT to improve the current understanding of OPD in CRPC patients.

2 MATERIALS AND METHODS

2.1 Patient Population

We identified patients using a robust prescribing database from a single academic oncology center. Patients who were treated with either abiraterone or enzalutamide for metastatic CRPC from April 1, 2015, to April 30, 2017, were included. For the purpose of this study, OPD was defined as ≤3 sites of the disease progressing radiologically as compared to baseline scan after an interim biochemical, radiological, or clinical response to treatment was demonstrated. Polyprogressive disease (Poly-PD) is conversely defined as >3 sites of the disease progressing while on ARTT, with or without initial response to ARTT.

Response was defined as a prostate-specific antigen (PSA) drop of >10% from baseline PSA as per the TRAP trial protocol (NCT036446303), or a scan showing radiological response or stable disease.

Data were collected using hospital electronic patient records. All imaging for OPD patients was reviewed by an experienced consultant radiologist or nuclear medicine (NM) physician, both of whom have experience in prostate cancer imaging.

Patients were included if they had been on ARTT off trial and had radiological, biochemical, or clinical progression while on ARTT or had stopped ARTT due to other reasons such as toxicity or other medical conditions. Patients were excluded if they did not receive or had not yet progressed on ARTT. Data for those patients treated within the TRAP trial (NCT036446303), a phase II trial assessing SBRT to OPD in CRPC patients, were excluded from the time of trial entry.

2.2 Definition of Progression

Oligoprogression was radiologically defined using a combination of adapted Prostate Cancer Working Group 3 (PCWG3) (17), Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (18), and Metastasis Reporting and Data System for Prostate Cancer (METRADS-P) (19). This reflects the range of imaging performed in a "real world" scenario.

For CT, it is the development of any new lesion or ≥20% increase in diameter of an existing lesion compared to the nadir or baseline CT scan; for bone scan, 2 or more new bone lesions or worsening of an existing lesion with a rising PSA on NM bone scan; for MRI, new or recurrent lesion compared to the nadir, unequivocal increase in size compared to a baseline scan, or regions with high signal intensity on high b value images on WBDWMRI; and for PET, any new avid lesion with standardized uptake value (SUV) above background or >20% increase in SUV max, compared to baseline/nadir scan on PET/CT, as used in clinical practice (18–20).

Further progression beyond OPD was defined as any further growth of OPD lesions or other lesions on CT, increase in SUV on PET/CT, or changes in signal intensity on WBDWMRI scans suggesting further progression and/or appearance of any new lesions compared to nadir/baseline scan, associated with PSA progression.

PSA progression was defined as a PSA increase of 25% from the nadir plus an absolute increase of 2 ng/ml, as per PCWG guidelines (17).

2.3 Definition of Endpoints

PFS 1 (PFS1) was defined as the time from starting ARTT to radiological progression or censored to the last follow-up.

PFS 2 (PFS2) was defined as the time between OPD detection and further radiological progression or death or censored to the last follow-up.

SBRT suitability of OPD lesions was determined by proximity to critical structures, size of lesion <6 cm, and index lesion not previously being irradiated.

OS was defined as the time from progression on ARTT to death of any cause or censored to the last follow-up.

PSA doubling time was calculated using the nadir PSA after starting ARTT and PSA at diagnosis of OPD.

Data were analyzed using the Kaplan–Meier survival curves and log-rank tests, and univariate and multivariate logistic regression using GraphPad version 9.0.

3 RESULTS

3.1 All Patients on Androgen Receptor-Targeted Therapy

A total of 102 patients met the inclusion/exclusion criteria. All patients initiated ARTT off trial for CRPC. The median follow-up from starting ARTT was 35.7 months.

Baseline characteristics for patients at initial diagnosis and at starting ARTT are summarized in **Tables 1**, **2**. Characteristics at the time of progression, stratified by OPD vs. Poly-PD criteria, are shown in **Table 3**.

TABLE 1 | Baseline characteristics at initial diagnosis.

Characteristics at initial diagnosis	N = 102
Age (years), n (%)	
Median (IQR)	67 (61–73)
≤60	22 (22)
61–70	44 (43)
>70	36 (35)
NCCN stage, n (%)	
Very low	1 (1)
Low	0
Intermediate	15 (15)
High	32 (32)
Very high	20 (20)
Metastatic	34 (33)
PSA (ng/ml), n (%)	
Mean (± SD)	227 ± 812
<10	23 (22)
10–20	22 (22)
>20	57 (56)
Primary radical treatment, n (%)	
Radical prostatectomy	11 (11)
Radical radiotherapy plus ADT	60 (59)
Postoperative radiotherapy	2 (2)
HIFU	1 (1)

ARTT, androgen receptor-targeted therapy; PSA, prostate-specific antigen; IQR, interquartile range; NCCN, National Comprehensive Cancer Network; ADT, androgen deprivation therapy; HIFU, high-intensity focus ultrasound.

TABLE 2 | Characteristics at starting ARTT.

Characteristics at starting ARTT	N = 102
Age years, n (%)	
Median (IQR), years	77 (71–82)
≤60 years	3 (3)
61–70 years	17 (17)
>70 years	82 (80)
Mean PSA, ng/ml (± SD)	171 ± 602
Prior docetaxel, n (%)	
Yes	8 (8)
No	94 (92)
Line of metastatic therapy, n (%)*	
2nd line	37 (36)
3rd line	32 (32)
4th line	33 (32)
ARTT treatment, n (%)	
Abiraterone	62 (60)
Enzalutamide	40 (40)

ARTT, androgen receptor-targeted therapy; PSA, prostate-specific antigen; IQR, interquartile range.

**Lines of therapy include treatments such as luteinizing hormone-releasing hormone agonists or antagonists (LHRH), combined androgen blockade, dexamethasone, and docetaxel chemotherapy.*

3.2 Oligoprogressive Disease Patients

Of the 102 patients, 82 (80%) had radiological evidence of progression, and 30 (29%) patients progressed with ≤3 sites (OPD) with 46 lesions in total, based on WBDWMRI, choline PET/CT, CT, or bone scan (**Table 4**). The most common sites of

TABLE 3 | Characteristics at progression on ARTT; OPD vs. Poly-PD.

Characteristics at progression	OPD, N = 30	Poly-PD, N = 52
Age (years), n (%)		
Median (IQR), years	75 (70–83)	79 (72–83)
≤60	1 (3)	1 (2)
61–70	7 (23)	8 (15)
>70	22 (73)	43 (83)
PSA mean, ng/ml (± SD)		
At prostate cancer diagnosis	120 ± 236	360 ± 1,100
At starting ARTT	63 ± 129	191 ± 751
At progression	15 ± 14	168 ± 434
Prior docetaxel, n (%)		
Yes	2 (7)	2 (4)
No	28 (93)	50 (96)
Line of therapy, n (%)		
2nd line	12 (40)	19 (37)
3rd line	12 (40)	14 (26)
4th line	6 (20)	19 (37)
ARTT treatment, n (%)		
Abiraterone	21 (70)	33 (63)
Enzalutamide	9 (30)	19 (37)

ARTT, androgen receptor-targeted therapy; PSA, prostate-specific antigen; IQR, interquartile range; OPD, oligoprogressive disease; WBDWMRI, whole-body diffusion-weighted MRI.

OPD were in bone lesions (20). Five patients had prostate oligoprogression (**Figure 1**).

The majority of the OPD lesions (36/46, 78%) were suitable for SBRT; 21/30 (70%) patients had all OPD sites suitable for SBRT. The reasons for lesions not being suitable for SBRT included the following: previously irradiated lesions (n = 4, 9%); lesions too large for SBRT in the liver, ischial bone metastasis, and para-spinal soft tissue mass (n = 3, 6%); ill-defined lesions in 2 patients with disease in Gerota's fascia and disease encasing the right ureter (n = 2, 4%); and a single lesion that required urgent radiotherapy (RT) to spinal disease causing nerve root compression (n = 1, 2%). Two-thirds of patients (20, 70%) with OPD had oligometastatic disease (defined as ≤5 lesions) at initial diagnosis. At the time of starting ARTT, the prevalence of oligometastatic disease had reduced to 12 (40%) patients.

3.2.1 Progression-Free Survival 2 (From Oligoprogressive Disease to Further Progression/Death)

Twenty-seven of 30 (90%) OPD patients were followed up with imaging bone scan and CT scan, WBDWMRI, or PET/CT (**Table 4**). Three patients had no follow-up imaging due to no PSA progression after switching from prednisolone to dexamethasone (1), death (1), and treatment elsewhere (1). The median time to the next follow-up scan after OPD is 13.1 months.

A small proportion of patients (8/30, 27%) had RT to OPD sites; 3 (10%) were treated within the TRAP trial, and data from trial entry have been excluded from the results. Three of the 5 patients treated off trial received SBRT (30 Gy in 3–5 fractions) to lymph nodes and bone metastasis, and 2 patients received palliative RT: one patient received 24 Gy in 4 fractions to the prostate, and the other patient received 20 Gy in 5 to the sacrum. The median PFS2 in those patients treated with RT was 13.6 months (n = 5), and in patients who did not receive RT for OPD

TABLE 4 | Characteristics of OPD patients.

Characteristics of OPD patients	OPD N = 30
NCCN stage at diagnosis, n (%)	
Intermediate	4 (13)
High	7 (23)
Very high	11 (37)
Metastatic	8 (27)
Primary radical treatment, n (%)	
Radical prostatectomy	5 (17)
Radical radiotherapy plus ADT	16 (53)
Postoperative radiotherapy	4 (13)
Salvage prostatectomy	2 (7)
Synchronous metastases, n (%)	8 (27)
Metachronous metastases	22 (73)
Oligometastatic (at initial metastatic diagnosis)	20 (67)
Polymetastatic	10 (33)
Oligometastatic at starting ARTT, n (%)	12 (40)
Polymetastatic at starting ARTT, n (%)	18 (60)
Number of OPD lesions, n (%)	
1 lesion	17 (57)
2 lesions	10 (33)
3 lesions	3 (10)
Scan detecting OPD, n (%)	
WBDWMRI	6 (20)
Choline PET/CT	6 (20)
CT	16 (53)
Bone scan	2 (7)
1st follow-up scan after diagnosis of OPD, n (%)	
WBDWMRI	5 (17)
Choline PET/CT	4 (13)
CT	8 (27)
Bone scan	1 (3)
CT and bone scan	4 (13)
TRAP trial imaging	3 (10
MRI pelvis	2 (7)
No imaging	3 (0)

ADT, androgen deprivation therapy; ARTT, androgen receptor-targeted therapy; NCCN, National Comprehensive Cancer Network; OPD, oligoprogressive disease; PSA, prostate-specific antigen; IQR, interquartile range; WBDWMRI, whole-body diffusion-weighted MRI.

but continued ARTT alone, it was 5.7 months (n = 16). There was no overt difference between the two groups, with log-rank HR 0.8 (95% CI 0.3–2.1), p = 0.68 (**Figure 2**).

Of the 5 patients who received RT to OPD, PFS2 was shorter for the 2 patients who received palliative RT doses compared to the 3 patients who received radical SBRT doses (7.6 vs. 21.4 months, respectively), p = 0.039. One patient who received 24 Gy in 4 fractions discontinued enzalutamide after commencing RT. Four out of the 5 patients had a high burden of disease defined as >3 known sites of the disease since initial prostate cancer diagnosis (i.e., not oligometastatic disease); however, only OPD sites were irradiated.

Of the five patients who had RT to OPD, one patient treated for prostate OPD had no further imaging performed; this patient had oligometastatic disease. Two patients eventually progressed in ≤3 sites (repeat OPD): one patient had re-occurrence in the irradiated sacrum (treated with 20 Gy in 5 fractions), and the other patient who received SBRT to a para-aortic lymph node received repeat SBRT to two more oligoprogressing lymph nodes. Two patients who received RT to OPD lesions in the prostate and the lymph nodes (para-aortic and common iliac) progressed with Poly-PD subsequently.

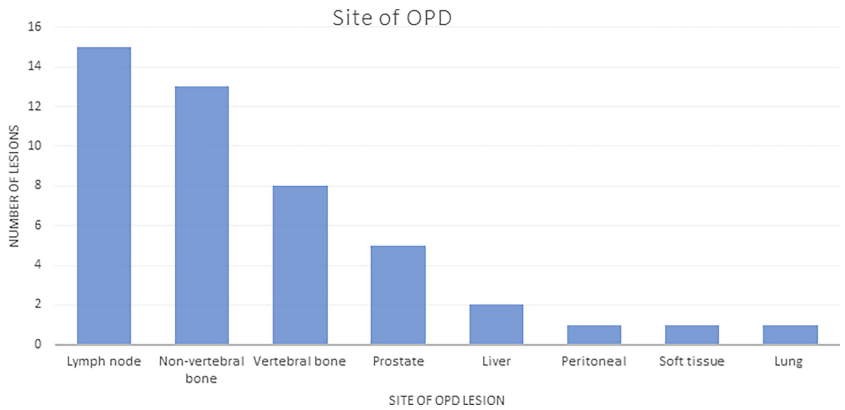

FIGURE 1 | Sites of OPD: number of lesions listed by site (total number of lesions in patients with OPD = 46). OPD, oligoprogressive disease.

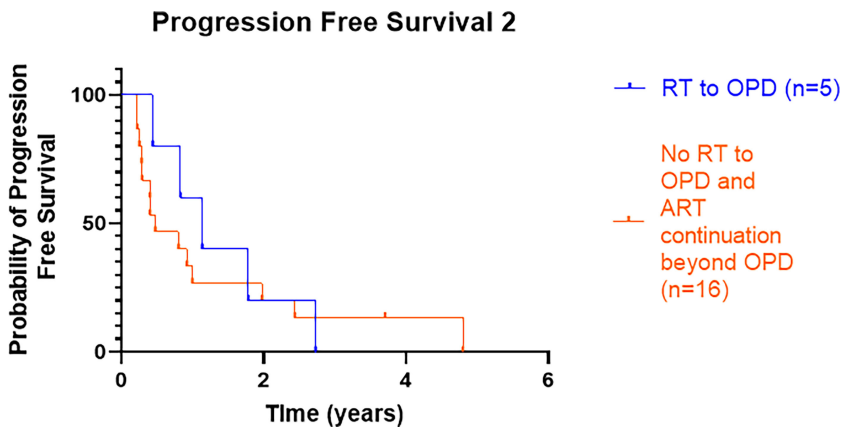

FIGURE 2 | Kaplan–Meier curve presenting PFS2 from OPD to further radiological progression or death for those patients treated with RT with or without continuation of ARTT or continuation of ARTT alone. PFS2, progression-free survival 2; OPD, oligoprogressive disease; RT, radiotherapy; ARTT, androgen receptor-targeted therapy.

Of the 16 patients who did not receive RT but continued ARTT, 8 (50%) patients had further OPD (i.e., ≤3 lesions including original OPD lesion progressing) on subsequent radiological imaging, and one of these patients subsequently was treated within the TRAP trial. Five (31%) patients had Poly-PD, and 3 (19%) patients had not radiologically progressed.

Six (28%) patients not treated with RT did not continue ARTT beyond OPD.

3.3 Oligoprogressive Disease Versus Polyprogressive Disease

Fifty-two (51%) patients had radiological evidence of Poly-PD with >3 sites of progression. The remaining 20 patients stopped ARTT due to reasons including PSA progression alone without imaging, toxicity, or death due to other causes. Five patients (10%) with Poly-PD continued ARTT beyond progression.

3.3.1 Progression-Free Survival 1 (Starting Androgen Receptor-Targeted Therapy to Radiological Progression)

Median PFS1 was 16.8 months in patients with OPD, while the median time to Poly-PD from starting ARTT was 11.7 months, with no overt difference, log-rank HR 0.84 (95% CI 0.53–1.3), p = 0.43 (**Figure 3**).

3.3.2 Overall Survival: Oligoprogressive Disease Versus Polyprogressive Disease

Median OS was similar in patients with prostate, lymph node, or bone OPD: prostate (23 months), lymph node (24.7 months), and bone (24 months) but better than visceral OPD (16.5 months), with no overt difference between each site (p = 0.19). One patient presented with OPD within the liver but progressed rapidly within 6 weeks with widespread progression.

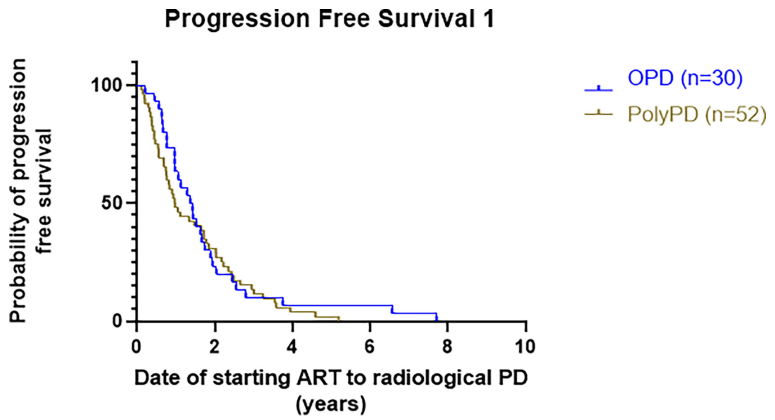

FIGURE 3 | Kaplan–Meier curve presenting PFS1 of patients with OPD versus Poly-PD. PFS1 is calculated as time from starting ARTT to either OPD or Poly-PD. PFS1, progression-free survival 1; OPD, oligoprogressive disease; Poly-PD, polyprogressive disease; ARTT, androgen receptor-targeted therapy.

Median OS in the RT group was 22.9 months (53 months in the SBRT only group). In patients receiving no RT, the median OS for those who continued ARTT vs. no continuation of ARTT was 27.2 vs. 16.3 months, p = 0.03 (**Figure 4**).

3.4 Prostate-Specific Antigen Kinetics: Oligoprogressive Disease Versus Polyprogressive Disease

The median [interquartile range (IQR)] PSA doubling time prior to progression was similar in both the OPD group at 5.5 (3.9–8.8) months and the Poly-PD group at 5.2 (2.9–9.3) months. The PSA response to ARTT in the OPD group was better than in the Poly-PD group with a median (IQR) percentage reduction of 89% (67%–95%) in the OPD group as compared to 70% (40%–84%) in the Poly-PD group. Of the 5 patients who received RT off trial for OPD, one patient who received SBRT did not have a PSA response but remained radiologically stable on ARTT for 21 months.

Both univariate and multivariate logistic regression analyses indicated an association between OPD and percentage PSA decline at the nadir with an odds ratio (OR) of 0.028 (CI 0.002–0.20), p < 0.0001. There was no overt association found with age, OPD, PSA doubling time, line of therapy, National Comprehensive Cancer Network (NCCN) stage at diagnosis, and type of ARTT.

3.5 Summary

In this study, 86 patients who progressed on ARTT had imaging available at the time of progression. Thirty (35%) of these patients presented with OPD during their ARTT treatment course. A substantial proportion of patients on ARTT (23%) had OPD lesions suitable for treatment with SBRT and would

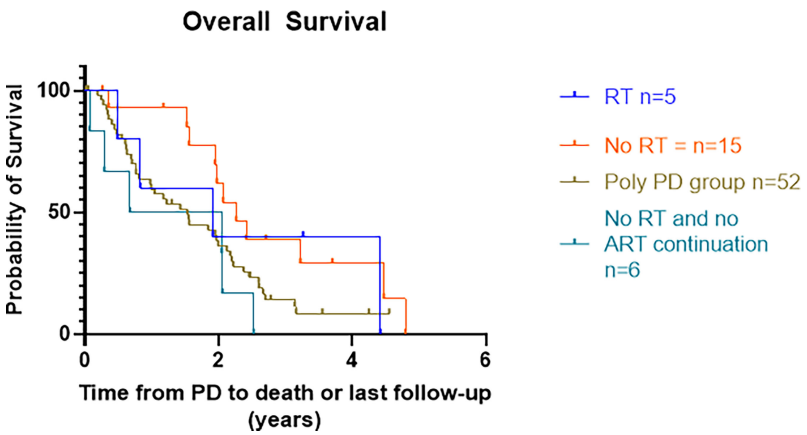

FIGURE 4 | Kaplan–Meier curves presenting OS from date of progression on ARTT to death or last treatment groups. OS, overall survival; ARTT, androgen receptor-targeted therapy.

have potentially been eligible for entry into the TRAP trial, a prospective phase II single-arm study.

4 DISCUSSION

MDT for OPD is an evolving treatment paradigm with no prospective or retrospective evidence as compared with the standard of care in prostate cancer patients. Despite this, some patients receive MDT for OPD in this clinical setting, although within the United Kingdom, SBRT for OPD is not yet commissioned.

Median PFS2 was >11 months longer in the SBRT plus ARTT patients as compared to ARTT alone for OPD, with a median PFS2 of 17.2 months. The numbers in this cohort, however, are very small; therefore, it is difficult to draw any conclusions. However, this reflects real-world practice where patients are being treated with RT for OPD, highlighting the need for a randomized control trial. Furthermore, a substantial number of OPD patients continued ARTT beyond OPD compared to those who continued beyond Poly-PD. This practice is in keeping with PCWG3 guidance (17) to continue ARTT until no further symptomatic benefit or until significant radiological progression. The difference in median OS between patients who continued ARTT beyond OPD (without MDT) and Poly-PD was >5 months, suggesting that ARTT alone beyond OPD may improve patient outcomes, and therefore, a trial comparing continuation of ARTT with vs. without SBRT for OPD is crucial in determining the magnitude of effect.

Data from retrospective studies to date have reported minimal toxicity, with 2 studies reporting 2 patients with grade 3 toxicity and no studies reporting ≥grade 4 toxicity (21–25). Deek et al. (26) in a retrospective series including 68 patients treated with MDT for OPD reported the time to next intervention as 15.6 months (systemic or further RT) and a median distant metastasis-free survival of 10.8 months. Fifty-five (80.9%) patients stayed on the same systemic therapy at the time of MDT. However, all patients included had MDT to OPD ± non-OPD sites. Fifty (74%) patients had ≤3 metastatic sites (i.e., oligometastatic disease) at baseline. A multicenter retrospective study by Detti et al. (22) included 32 patients on abiraterone, not suitable for chemotherapy, treated with RT to OPD lesions or for palliative intent to treat symptoms, and median PFS2 was 9.6 months. A retrospective multicenter study by Triggiani et al. (27) included 86 patients with bone or lymph node OPD lesions (up to 5) treated with SBRT for patients on 1st-line treatment with ADT. The study found a median new metastasis-free survival of 12.3 months, with 26 of the patients undergoing further SBRT. The studies all suggest a prolonged progression-free interval after SBRT to sites of OPD. However, there is marked heterogeneity among these trials with regard to inclusion criteria and RT administration, highlighting the lack of consensus on defining and therefore treating OPD patients. There is also no comparison to the standard of care to determine the magnitude of benefit. This is needed to ensure that the apparently encouraging PFS2 intervals are not solely due to optimal case selection.

A difference between median OS in the SBRT group (53 months) and those with OPD and no continuation of ARTT (16.3 months) within this study could also be due to selection bias. Patients clinically deteriorating would not have been suitable for SBRT and therefore favored to switch to a different systemic therapy or best supportive care, with asymptomatic patients with a better performance status more likely to be treated with SBRT.

Twelve patients found to have OPD within this study were identified on functional imaging such as PET/CT or WBDWMRI instead of standard imaging using CT or bone scans. These scanning methods are not the standard of care in the United Kingdom; however, they are considered useful in the early detection of OPD in clinical practice. Yoshida et al. (23) studied 23 patients with CRPC who underwent WBDWMRI scans identifying OPD, which were then treated with RT doses ranging from 60 to 78 Gy (2 Gy per fraction) to the prostate/lymph node metastasis and 30 to 39 Gy (2–3 Gy per fraction) to bone metastases. The study reported the median time to PSA failure to be 8.7 months. However, there is no comparison with standard CT and bone scan imaging. Detection of progression on bone scan is notoriously difficult, hence the interest in next-generation imaging such as WBDWMRI and PET/CT. Although these imaging modalities are impacting patient treatment decisions, the significance of early detection on these scans is not known. Defining the eligibility imaging required for a randomized trial will likely set the standard going forward.

Patients with OPD had a significantly lower PSA at the nadir on ARTT, with a median reduction in PSA > 20% than in patients with Poly-PD. Median time on ARTT before progressing was also 5 months longer in patients presenting with OPD compared to Poly-PD. These data suggest that OPD may be more prevalent in those patients who have had a significant and sustained PSA response to ARTT. Close imaging surveillance of these patients may help to identify OPD, facilitating MDT before widespread metastatic disease develops. Surprisingly, PSA doubling time at progression did not predict OPD. A lower median PSA at the nadir in the OPD group of 2.6 vs. 9 in the Poly-PD group may have obscured the effect of PSA doubling time, with the OPD group requiring a smaller overall rise to double as compared to the Poly-PD group. Larger datasets are required before PSA response criteria identifying likely OPD can be proposed.

PSA change in response to RT within this study was not a useful biomarker predicting response to MDT. Circulating tumor DNA (ctDNA) may be a more discriminatory marker in predicting response to SBRT, in combination with PSA results, and is a necessary component of any prospective trial to ensure appropriate patients are selected for treatment (28).

We acknowledge that there are a number of limitations, with this study being retrospective. The study includes a small number of heterogeneous patients treated with RT; therefore, this limits the strength of the conclusions drawn. Treatment paradigms were not protocolized; hence, the imaging and RT delivered are varied, and outcomes may reflect selection bias rather than underlying biology. The study reflects real-world practice and highlights characteristics within a cohort of patients who may be eligible for treatment with SBRT and helps to delineate the population for further study.

TABLE 5 | Summary of clinical trials in progress utilizing metastasis-directed therapy for oligoprogression metastatic prostate cancer.

Clinical trial	Phase	N	OPD definition	Treatment arms	Systemic therapy at the time of OPD	Primary outcome	Estimated study completion date	Clinical trials.gov identifier
TRAP	II	84	1–2 OPD lesions in bone, lymph node, prostate, or lung	SBRT to OPD lesions and continuation of ARTT	Enzalutamide/abiraterone	PFS	February 2022	NCT036446303
IOSCAR	Pilot	40	1–3 new or OPD lesions or oligopersistent lesions in bone or lymph node	SBRT to oligorecurrent alone or OPD + ADT	ADT for OPD No ADT for oligorecurrent disease	Immune response evaluation	October 2024	NCT04624828
MEDCARE	II	18	≤3 extracranial metastases or local recurrence	SBRT or metastatectomy to OPD lesion and continuation of systemic therapy	ADT alone or in combination with another systemic therapy	Next-line systemic treatment-free survival and PSMA PET-CT accuracy and predictive value	January 2030	NCT04222634
NCT04838899	I	30	≤5 OPD lesions or PSA progression only in the setting of oligometastases (≤5 metastatic lesions). With ≤3 metastases in one organ	SBRT + abiraterone	Abiraterone	SBRT-related toxicity and PFS	December 2025	NCT04838899

ARTT, androgen receptor-targeted therapy; OPD, oligoprogressive disease; SBRT, stereotactic body radiotherapy; ADT, androgen deprivation therapy; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; OPD, oligoprogressive disease.

Ongoing clinical trials include the TRAP trial (NCT036446303) treating CRPC patients on ARTT with SBRT to up to 2 OPD lesions, with a biomarker assessment panel evaluating the use of WBDWMRI and ctDNA in predicting response. MEDCARE (NCT 04222634) is a phase II study assessing the role of prostate-specific membrane antigen (PSMA) PET-CT in OPD, which may tell us which patients would benefit from SBRT to OPD in CRPC (**Table 5**). With patients now accessing ARTT in the hormone-sensitive setting (29), the question of whether RT can improve progression-free and OS needs to include patients progressing on first-line therapy, to ensure the relevance of conclusions for future patients.

Oligoprogression is common in a real-world setting. We identified a subgroup of patients potentially suitable for a novel treatment strategy including SBRT. Ongoing trials will help identify predictive biomarkers, but a randomized trial is needed to establish if there is a clinically significant benefit after SBRT.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data sharing will need to be requested through the official hospital channels. Requests to access the datasets should be directed to PP.

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PP project development, data collection, data analysis, and manuscript writing. NT and DL: radiology review, data collection, and manuscript writing. CP, JM, AP, AR, NvA, RE, VK, and JdB manuscript writing. AT: project development and manuscript writing. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. AT acknowledges support from Prostate Cancer UK, Cancer Research UK (C33589/A28284 and C7224/A28724 CRUK RadNet), and the JP Moulton Foundation. All authors: this project represents independent research supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London.

REFERENCES

1. CRUK. *Cancer Research UK* (2020). Available at: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/risks-causes.
2. Ng K, Wilson P, Mutsvangwa K, Hounsome L, Shamash J. Overall Survival of Black and White Men With Metastatic Castration-Resistant Prostate Cancer (mCRPC): A 20-Year Retrospective Analysis in the Largest Healthcare Trust in England. *Prostate Cancer Prostatic Dis* (2021) 24:718–24. doi: 10.1038/s41391-020-00316-x
3. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in Metastatic Prostate Cancer Without Previous Chemotherapy. *N Engl J Med* (2013) 368(2):138–48. doi: 10.1056/NEJMoa1209096
4. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone Plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* (2017) 377(4):352–60. doi: 10.1056/NEJMoa1704174
5. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in Metastatic Prostate Cancer Before Chemotherapy. *N Engl J Med* (2014) 371(5):424–33. doi: 10.1056/NEJMoa1405095
6. Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, Miller K, et al. Increased Survival With Enzalutamide in Prostate Cancer After Chemotherapy. *N Engl J Med* (2012) 367(13):1187–97. doi: 10.1056/NEJMoa1207506
7. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer. *N Engl J Med* (2011) 364(21):1995–2005. doi: 10.1056/NEJMoa1014618
8. Penning TM. Mechanisms of Drug Resistance That Target the Androgen Axis in Castration Resistant Prostate Cancer (CRPC). *J Steroid Biochem Mol Biol* (2015) 153:105–13. doi: 10.1016/j.jsbmb.2015.05.010
9. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic Ablative Radiotherapy Versus Standard of Care Palliative Treatment in Patients With Oligometastatic Cancers (SABR-COMET): A Randomised, Phase 2, Open-Label Trial. *Lancet (London England)* (2019) 393 (10185):2051–8. doi: 10.1016/S0140-6736(18)32487-5
10. Gomez DR, Blumenschein GR, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local Consolidative Therapy Versus Maintenance Therapy or Observation for Patients with Oligometastatic Non-Small-Cell Lung Cancer Without Progression After First-Line Systemic Therapy: A Multicentre, Randomised, Controlled, Phase 2 Study. *Lancet Oncol* (2017) 17(12):1672–82. doi: 10.1016/S1470-2045(16)30532-0
11. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, DeBruycker A, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol* (2018) 36(5):446–53. doi: 10.1200/JCO.2017.75.4853
12. Turpin A, Girard E, Baillet C, Pasquier D, Olivier J, Villers A, et al. Imaging for Metastasis in Prostate Cancer: A Review of the Literature. *Front Oncol* (2020) 10:55. doi: 10.3389/fonc.2020.00055
13. Basler L, Kroeze SGC, Guckenberger M. SBRT for Oligoprogressive Oncogene Addicted NSCLC. *Lung Cancer* (2017) 106:50–7. doi: 10.1016/j.lungcan.2017.02.007
14. Aitken K, Tree A, Thomas K, Nutting C, Hawkins M, Tait D, et al. Initial UK Experience of Stereotactic Body Radiotherapy for Extracranial Oligometastases: Can We Change the Therapeutic Paradigm? *Clin Oncol* (2015) 27:411–9. doi: 10.1016/j.clon.2015.03.006
15. Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA, et al. Stereotactic Body Radiotherapy for Oligometastases. *Lancet Oncol* (2013) 14 (1):e28–37. doi: 10.1016/S1470-2045(12)70510-7
16. Ost P, Jereczek-Fossa BA, Van A, Zilli T, Muacevic A, Olivier K, et al. Progression-Free Survival Following Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Treatment-Naive Recurrence: A Multi-Institutional Analysis. *Eur Urol* (2016) 69(1):9–12. doi: 10.1016/j.eururo.2015.07.004
17. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol* (2016) 34(12):1402–18. doi: 10.1200/JCO.2015.64.2702
18. Schwartz LH, Litière S, De Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-Update and Clarification: From the RECIST Committee HHS Public Access. *Eur J Cancer* (2016) 62:132–7. doi: 10.1016/j.ejca.2016.03.081
19. Padhani AR, Lecouvet FE, Tunariu N, Koh D-M, De Keyzer F, Collins DJ, et al. METastasis Reporting and Data System for Prostate Cancer: Practical Guidelines for Acquisition, Interpretation, and Reporting of Whole-Body Magnetic Resonance Imaging-Based Evaluations of Multiorgan Involvement in Advanced Prostate Cancer. *Eur Urol* (2017) 71(1):81–92. doi: 10.1016/j.eururo.2016.05.033
20. Scher HI, Morris MJ, Basch E, Heller G. End Points and Outcomes in Castration-Resistant Prostate Cancer: From Clinical Trials to Clinical Practice. *J Clin Oncol* (2011) 29(27):3695–704. doi: 10.1200/JCO.2011.35.8648
21. Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, et al. Efficacy of Stereotactic Body Radiotherapy in Oligorecurrent and in Oligoprogressive Prostate Cancer: New Evidence From a Multicentric Study. *Br J Cancer* (2017) 116(12):1520–5. doi: 10.1038/bjc.2017.103
22. Detti B, D'Angelillo RM, Ingrosso G, Olmetto E, Francolini G, Triggiani L, et al. Combining Abiraterone and Radiotherapy in Prostate Cancer Patients Who Progressed During Abiraterone Therapy. *Anticancer Res* (2017) 37 (7):3717–22. DOI: 10.21873/anticanres.11744
23. Yoshida S, Takahara T, Arita Y, Ishii C, Uchida Y, Nakagawa K, et al. Progressive Site-Directed Therapy for Castration-Resistant Prostate Cancer: Localization of the Progressive Site as a Prognostic Factor. *Int J Radiat Oncol Biol Phys* (2019) 105(2):376–81. doi: 10.1016/j.ijrobp.2019.06.011
24. Valeriani M, Detti B, Fodor A, Caini S, Borghesi S, Trippa F, et al. Radiotherapy at Oligoprogression for Metastatic Castration-Resistant Prostate Cancer Patients: A Multi-Institutional Analysis. *Radiol Med* (2022) 127:108–16. doi: 10.1007/s11547-021-01424-x
25. Berghen C, Joniau S, Ost P, Poels K, Everaerts W, Decaestecker K, et al. Progression-Directed Therapy for Oligoprogression in Castration-Refractory Prostate Cancer. *Eur Urol Oncol* (2021) 4(2):305–9. doi: 10.1016/j.euo.2019.08.012
26. Deek MP, Taparra K, Phillips R, Velho PI, Gao RW, Deville C, et al. Metastasis-Directed Therapy Prolongs Efficacy of Systemic Therapy and Improves Clinical Outcomes in Oligoprogressive Castration-Resistant Prostate Cancer. *Eur Urol Oncol* (2021) 4(2):30–309. doi: 10.1016/j.ijrobp.2020.07.501
27. Triggiani L, Mazzola R, Magrini SM, Ingrosso G, Borghetti P, Trippa F, et al. Metastasis-Directed Stereotactic Radiotherapy for Oligoprogressive Castration-Resistant Prostate Cancer: A Multicenter Study. *World J Urol* (2019) 37(12):2631–7. doi: 10.1007/s00345-019-02717-7
28. Salami SS, Singhal U, Spratt DE, Palapattu GS, Hollenbeck BK, Schonhoft JD, et al. Circulating Tumor Cells as a Predictor of Treatment Response in Clinically Localized Prostate Cancer. *JCO Precis Oncol* (2019) 3):1–9. doi: 10.1200/PO.18.00352
29. James N, de Bono J, Spears M, Clarke N, Dearnaley D, Ritchie A, et al. Abiraterone for Prostate Cancer Not Previously Treated With Hormone Therapy. *N Engl J Med* (2017) 377(4):338–51. doi: 10.1056/NEJMoa1702900

Author Disclaimer:: The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

Conflict of Interest: AT has received research funding and/or travel funding from Elekta, Varian, and Accuray, and honoraria/travel budget support from Janssen and historically from Astellas. AP has received research funding from Elekta and honoraria from Elekta and Janssen. JB has served on advisory boards and received fees from many companies including Amgen, Astra Zeneca, Astellas, Bayer, Bioxcel Therapeutics, Boehringer Ingelheim, Cellcentric, Daiichi, Eisai, Genentech/Roche, Genmab, GSK, Harpoon, ImCheck Therapeutics, Janssen, Merck Serono, Merck Sharp & Dohme, Menarini/Silicon Biosystems, Orion, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Terumo, and Vertex Pharmaceuticals. He is an employee of ICR and has received funding or other support for his research work from AZ, Astellas, Bayer, Cellcentric, Daiichi, Genentech, Genmab, GSK, Janssen, Merck Serono, MSD, Menarini/Silicon Biosystems, Orion, Sanofi Aventis, Sierra Oncology, Taiho, Pfizer, and Vertex, which has a commercial interest in abiraterone, PARP inhibition in DNA repair defective cancers, and PI3K/AKT pathway inhibitors (no personal income). JB was named as an inventor, with no financial interest for patent 8,822,438, submitted by Janssen, that covers the use of abiraterone acetate with corticosteroids. He has been the CI/PI of many industry-sponsored clinical trials. JB is a National Institute for Health Research (NIHR) Senior Investigator. CP served on Bayer in the education steering committee on January 21, 2020. He received payment from ICR

for the podcast on mCRPC, July 2021; speaker fees from Janssen for Summit on Feb 2020, lecture on Nov 2020, and Ad board on March 2020; fees from Clarity Pharmaceuticals for Ad board on April 2020; fees from Myovant for Ad board on October 2020; fees from ITM Radiopharma for Ad board on October 2021; payment from AAA to ICR for Ad board on Dec 2021. RE declares receiving honorarium as a speaker at GU-ASCO Meeting 2016 and support from Janssen, as a speaker at the Royal Marsden NHS Foundation Trust 2017. She has received an honorarium as a speaker at the University of Chicago in 2018 and Bayer and Ipsen honoraria at the ESMO meeting in 2019, and she is a member of the external expert committee of AstraZeneca UK Limited. PP received an honorarium for educational cases for PinPoint Case Platform, Mirrors of Medicine, and research post funded by the Royal Marsden/Institute of Cancer Research Biomedical Research Centre and Prostate Cancer UK. N.J.V.A. declares consultant honorarium from Accuray and Research funds from Accuray. AR has received honoraria and travel support from Janssen, Astellas and AZD. VK reports honoraria for speakers bureaus, personal fees and non-financial support from Accuray, Astellas, Bayer, Boston Scientific, and Janssen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 24 May 2022
doi: 10.3389/fonc.2022.834023

Robot-Assisted Surgery vs Robotic Stereotactic Body Radiotherapy in Prostate Cancer: A Cost-Utility Analysis

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *12 December 2021*
Accepted: *22 April 2022*
Published: *24 May 2022*

Citation:
Farah L, Magne N, Martelli N, Sotton S, Zerbib M, Borget I, Scher N, Guetta T, Chargari C, Bauduceau O and Toledano A (2022) Robot-Assisted Surgery vs Robotic Stereotactic Body Radiotherapy in Prostate Cancer: A Cost-Utility Analysis. Front. Oncol. 12:834023. doi: 10.3389/fonc.2022.834023

Prostate cancer is the most common men cancer in France. Continuous progress in oncology led to develop robot-assisted Radical Prostatectomies (rRP) and robot-assisted stereotactic body radiotherapy (rSBRT). The present study aims at comparing economic and clinical impacts of prostate cancer treatments performed either with rSBRT or rRP in France. A Markov model using TreeAge Pro software was chosen to calculate annual costs; utilities and transition probabilities of localized prostate cancer treatments. Patients were eligible for radiotherapy or surgery and the therapeutic decision was a robot-assisted intervention. Over a 10-year period, rSBRT yielded a significantly higher number of quality-adjusted life years than rRP (8.37 vs 6.85). In France, rSBRT seemed more expensive than rRP (€19,475 vs €18,968, respectively). From a societal perspective, rRP was more cost-saving (incremental cost effectiveness ratio = €332/QALY). The model was sensitive to variations of costs of the initial and recurrence state in one-way sensitivity analyses. Robot-assisted stereotactic body radiotherapy seems more cost-effective than Radical Prostatectomy in terms of QALY despite the slightly higher initial cost due to the use of radiotherapy. It would be interesting to conduct comparative quality of life studies in France over longer periods of time.

Keywords: robot-assisted radical prostatectomy, prostate cancer, health economic analysis, quality of life, cost-utility analyses, stereotactic body radiation therapy (SBRT)

INTRODUCTION

Despite significant progress in early detection of prostate cancer, it remains the first leading cause of male cancer death in France with 8,512 deaths annually (1). It is responsible for nearly a quarter of all cancers and more than 50,430 new cases diagnosed yearly in France (1). The development of new surgical techniques and medical devices has offered new possibilities to treat this pathology.

The main therapeutic modalities for treating localized prostate cancer are external radiation treatments such as Intensity-Modulated Radiation Therapy (IMRT) as well as brachytherapy (or a combination of both) and surgery (radical prostatectomy). Stereotactic radiotherapy is one of the therapeutic standards recommended by the American Society for Radiation Oncology (ASTRO) (2) and the National Comprehensive Cancer Network (NCCN) (3) but, it has not yet been included in French guidelines. Some surgical teams have chosen robot-assisted surgery as a standard operating technique for localized prostate cancer. The surgeon still removes the prostate and the seminal vesicles but the intervention is enhanced by robotics (4). In parallel to these minimally invasive robot-assisted Radical Prostatectomy (rRP) procedures, there have also been recent advances in radiotherapy (5). The latest key innovation is the development of robot-assisted stereotactic body radiotherapy (rSBRT), with Cyberknife™ robot (Accuray) for instance. This non-invasive irradiation technique delivers a high dose to a small volume (6). The low toxicity of rSBRT and its capacity to improve quality of life make it at least comparable and as well tolerated as other radiotherapy techniques (such as proton therapy, brachytherapy or Intensity-modulated radiotherapy) (5). rSBRT is also an effective option for the elderly or to patients in whom surgery is contraindicated. To date, the economic and societal benefits of SBRT performed by Cyberknife still require a more extensive assessment over longer follow-up periods. In the USA, studies has shown that rSBRT is considered more cost-effective than IMRT (7). Reducing treatment duration would mean an improvement of patients' quality of life and a reduction in treatment costs (e.g. lower ambulance transportation costs). Moreover, robotic radiotherapy with Cyberknife uses artificial intelligence to localize tumours.

However, these different robot-assisted therapies have not been compared and the current European and French guidelines regarding low-risk localized prostate cancer (as defined by the D'Amico classification) do not favour one type of intervention over the other, even though localized prostate cancers represent 40 to 50% of all prostate cancers diagnosed in France (1).

Furthermore, surgical robots implemented in French operating theatres do not require any specific authorizations. As a result, the costs of a robot are negotiated by each hospital and are not covered by the French national health insurance scheme. Robot-assisted radical prostatectomies accounted for 73% of 20,380 procedures performed in France in 2018 (8). There is also a general lack of economic data to substantiate the additional costs and potential benefits of this technique. Consequently, an economic evaluation comparing these new therapies, in particular rRP and rSBRT, would permit to estimate their potential benefits for patients (at a clinical level) and institutions (at an economical level) and thereby, provide a tool to assist financial decision-makers.

MATERIALS AND METHODS

The current cost-utility analysis sought to understand the economic and long-term clinical impacts of treating prostate cancer with rSBRT rather than rRP, in France. In order to build our health economic model to compare both strategies, we created a Markov model structure with four states. For each state, we determined clinical inputs, quality of life relative to utilities and costs inputs. Finally, sensitivity analysis was performed to assess uncertainty of model parameters and robustness of the model.

Study Design

A Markov cost-effectiveness model was developed to compare incremental costs and quality-adjusted life years (QALYs) of rSBRT/rRP. The analysis was conducted from a societal perspective over a 10-year time horizon. It included costs related to interventions, side effects (affecting sexual, bowel and urinary functions as well as bleeding), medical visits, transportation and follow-up. The article was written according to the ISPOR CHEERS checklist (9).

The Markov Model Structure

Our model included two treatment strategies: robot-assisted radical prostatectomy and robotic stereotactic body radiotherapy. The model was constructed using 1-year cycles and estimated cost effectiveness for a period of up to 10 years. Within each cycle, patients could experience clinical events leading to recurrence or death and associated costs and quality of life (QoL) adjustments (**Figure 1**). The model differentiated four distinct states as recommended by the radiotherapeutic oncology team. An "Initial state" (patient's condition between the intervention and the first year following the intervention), a "1-year post-interventional state" (patient's condition after the first year of treatment) -added to take into account the lack of memory in a Markov model- a "recurrence" status (detected during routine follow-up, which could require surgery, radiation therapy or drug interventions or an increased number of follow-up consultations) and "Death".

One of our hypotheses was that over the 10-year time horizon of our model, the state of "distant metastasis" would not be modeled. Our model used the TreeAge Pro software (v2022). We calculated the annual costs *per* patient for each of the two treatment strategies and the utilities and transition probabilities between each state.

Clinical Inputs and Quality of Life

A team composed of radiation oncologists and urologists defined the target population. Low-risk localized (non-metastatic) prostate cancer cases as defined by the D'Amico classification (intracapsular

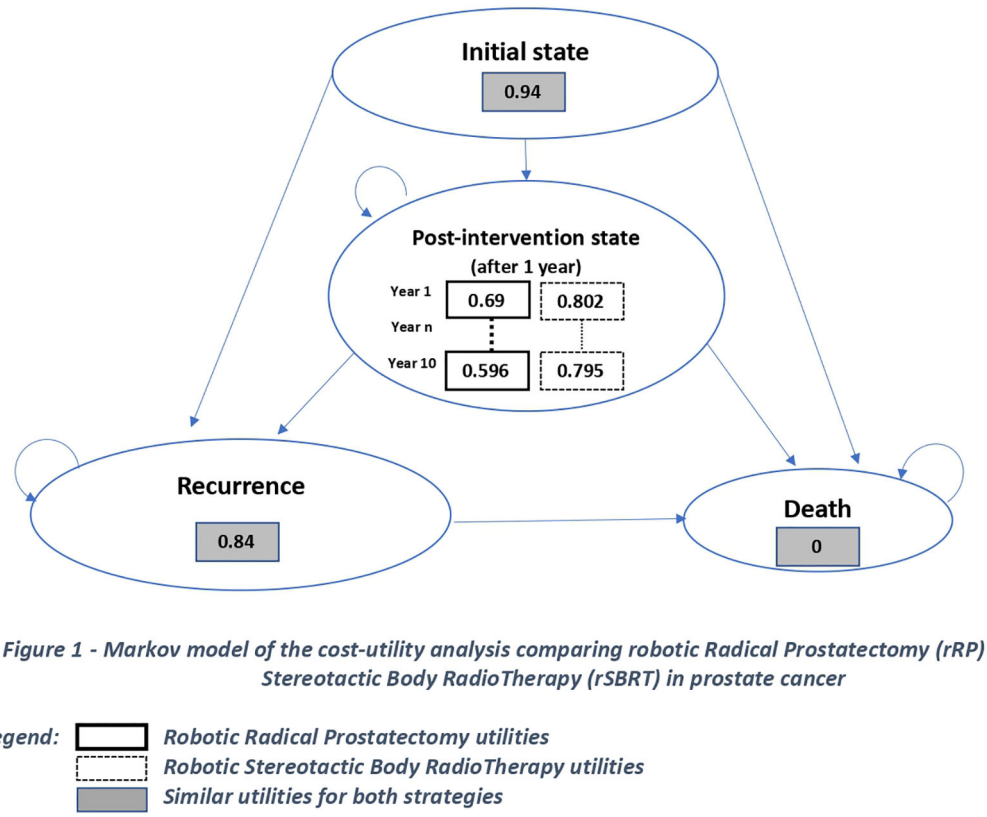

FIGURE 1 | Markov model of the cost-utility analysis comparing rRP and rSBRT in prostate cancer.

cancer (T1 or T2a), PSA <10 and Gleason score <7) were included [3]. The therapeutic decision discussed at a urology tumor board was a robot-assisted intervention (by surgery or by stereotactic radiotherapy). Patients were eligible for radiotherapy or surgery.

Within the model, we determined the probabilities of a transition between the different states as well as the costs and the utilities of each state (**Table 1**) (13). Individual parameter values were determined from a literature review performed on 08/01/2019 without period specification (Medline) and from medical experts' interviews. Articles selection and the flow chart are detailed in the **Supplementary File**. Utility values for each state were reported in the literature for prostate cancer patients (**Table 1**). The utilities, *i.e.* the units that estimate the quality of life, were found in the studies selected in our literature review. In the current analysis, utility values were compared to the corresponding baseline values obtained for prostate cancer patients prior to rRP or rSBRT (**Table 1**). The average utilities of the "post-intervention" state (**Table 1**) was estimated based on utility data reported in the literature and the patients' likelihood to experience sexual, urinary and bowel dysfunctions, compared to the baseline utility values established at the time the patient was included in the study (7). Utility values highlighted some aspects of quality of life that were elaborated in the prostate cancer specific quality of life questionnaires (Expanded Prostate Cancer Index Composite). Depending on the type of intervention, we compared values from the Katz et al. study (5), the PACE-B study (10) and the PROTECT trial (11) and the probability of occurrence of any adverse effects to calculate the average utility *per* year (5). Utility values decreased after intervention because they captured the decrement in QoL due to age but also due to the burden of prostate cancer, while the probability of death increased over the 10-year period. This decreasing utility values were consistent with the age-related decline of the general population reported in the French INSEE database (14).

Quality-adjusted life years (QALYs) were calculated by multiplying the length of time in a state by the utility for the given state. QALYs were discounted at an annual rate of 4% as recommended by the French Health Agency (15).

Costs Inputs

The analysis considered direct costs as well as costs associated with long-term disability care provided in facilities. Cost data was collated from multiple sources including the French Diagnosis Related Group (DRG) system for 2021 and published costs (**Table 1**) (12, 16). The cost data used in our model refers to French national data. Indeed, the DRGs correspond to the price of a hospitalization for prostatectomy or radiotherapy session in France

TABLE 1 | Summary of utilities, costs and transition probabilities of the different states calculated and collated for rRP and rSBRT.

UTILITIES & COSTS						
		rSBRT - robotic Stereotactic Body RadioTherapy		**rRP - robotic Radical Prostatectomy**		
States		**Costs (€)**	**Utilities**	**Costs (€)**	**Utilities**	**Sources**
Initial		€ 10,815	0.94 (CI_{95} = 0.90-0.98)	€ 8,881	0.94 (CI_{95} = 0.90-0.98)	Utility (5): Costs: details about initial costs calculation in table 2 of the Supplementary material B
Post-intervention » (after 1 year)	**Year 1**	€ 902	0.802 (CI_{95} = 0.752-0.852)	€ 902	0.69 (CI_{95} = 0.64-0.74)	Utility : Katz et al., PACE-B, PROTECT (5), (10), (11) Cost (12):
	Year 2		0.789 (CI_{95} = 0.739-0.839)		0.687 (CI_{95} = 0.637-0.737)	
	Year 3		0.795 (CI_{95} = 0.745-0.845)		0.719 (CI_{95} = 0.669-0.769)	
	Year 4		0.795 (CI_{95} = 0.745-0.845)		0.594 (CI_{95} = 0.476-0.714)	
	Year 5		0.795 (CI_{95} = 0.745-0.845)		0.603 (CI_{95} = 0.483-0.724)	
	Year 6+		0.795 (CI_{95} = 0.745-0.845)		0.596 (CI_{95} = 0.477-0.715)	
Recurrence		€ 13,707	0.84 (CI_{95} = 0.81-0.87)	€ 13,707	0.84 (CI_{95} = 0.79-0.89)	Utility (5): Cost (12):
		TRANSITION PROBABILITIES				
Transition		**Probabilities (%)**	**Sources**	**Probabilities (%)**	**Sources**	
Transition probability from «initial state» to « recurrence »		0.0011	[7]	0.00255	[20] + [10]	
Transition probability from « post-intervention » state (after 1 year) to « Recurrence »		0.0011	[7]	0.00255	[20] + [10]	
Transition probability from «initial state » to «Death»		0.00979	[11]	0.00979	[11]	

(regardless of the type of hospital). The details of the calculations specified in our **Supplementary File** correspond to the average national costs of prostate cancer treatment in France.

The "Initial state" costs were calculated from French databases for each type of intervention (**Supplementary File**) (16–21). All costs were in Euros for the year 2021. Future costs were discounted at an annual rate of 4% as recommended by the French Health Agency (15).

Sensitivity Analysis

Uncertainty of model parameters was assessed using one-way deterministic analysis and probabilistic sensitivity analyses. Treatment-specific inputs included all transition probabilities, costs and health utilities.

One-way sensitivity analysis assessed the impact on model outcomes from a variation of input parameters of -/+20% unless otherwise noted, which included 95% confidence intervals (CI). Probabilistic sensitivity analyses assessed the overall uncertainty in the values used in the model and were based on a Monte Carlo simulation of 1000 iterations of the model over a 10-year time frame. Results are reported as an incremental cost-effectiveness ratio (ICER).

Finally, we estimated the "willingness to pay" which is the estimate of the willingness of the French financial decision-maker, namely health insurance, to pay for an intervention rather than another. The patient does not pay for his treatment whose costs are covered 100% by the French health insurance. Therefore, the amount paid by health insurance was taken into account in the model.

TABLE 2 | Costs and QALYs (Quality Adjusted Life Years) differences between the two strategies (rRP versus rSBRT) in order to estimate the ICER (Incremental Cost Effectiveness Ratio) over a 10-year time horizon.

Strategy	Cost (€)	Incremental Cost (€)	QALY	Incremental QALY	ICER
robotic Radical Prostatectomy (rRP)	18,968		6.845		
robotic Stereotactic Body RadioTherapy (rSBRT)	19,475	507	8.373	1.528	332

RESULTS

Over a 10-year period, robotic stereotactic radiotherapy yielded a significantly higher number of QALYs than robot assisted radical prostatectomy (8.373 *vs* 6.845, respectively). However, in France, rSBRT seemed more expensive than rRP (€19,475 *vs* €18,968, respectively). This led to an incremental cost of €507 for rSBRT compared to rRP over a 10-year period (**Table 2**).

From a societal perspective, rRP was cost saving when compared to rSBRT (ICER = €332/QALY over a 10-year time horizon). The acceptability curve (**Figure 2**) highlighted that, over a 10-year period, rSBRT became more cost-effective than rRP, beyond the €710 threshold (corresponding to the "willingness to pay"), from a societal perspective.

One-Way Deterministic Sensitivity Analysis

One-way sensitivity analyses, depicted in the Tornado diagram (**Figure 3**), illustrated that the model was more sensitive to cost variations of the initial state, regardless of the type of intervention (rRP/rSBRT) and to cost variations of recurrence state. The utilities values and the time horizon, entitled "number of years in the model", had no significant impact on ICER. Therefore, the duration of the time horizon did not influence the results of our analysis.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analyses -the dispersion of 1,000 ICER simulations- indicated that these ICERs were distributed in the northeast quadrant. The cost-effectiveness of rSBRT *vs* rRP was generally robust to changes in input variables. Dispersion is low. The incremental QALY values range 1,51-1,56 and the incremental costs between €150 and €850 (**Figure 4**). In this scenario, robotic stereotactic radiotherapy is likely to be more effective, in terms of QALYs, and more expensive than robot-assisted radical prostatectomy over a 10-year time period.

DISCUSSION

Based on data from the scientific literature and the estimated costs of treatments in France, our study suggests that, from a societal perspective, the use of rSBRT could prove cost-effective compared to rRP. Despite the moderate cost differential favoring rRP over a 10-year horizon (€507), rSBRT appeared to significantly improve patients' quality of life (1.528 QALY corresponding to ICER €332/QALY). To our knowledge, this is the first economic evaluation that compares two robot-assisted curative robot-assisted interventions for the treatment of localized prostate cancer (rRP *vs* rSBRT). It is also the first economic evaluation that specifically addresses costs in France, unlike previous international studies (22). Our model is adapted to the French context but further studies should be conducted in other countries with suitable adaptations. This work could be repeated in another context to verify the generalization and robustness of these results. Even if rSBRT was not compared to

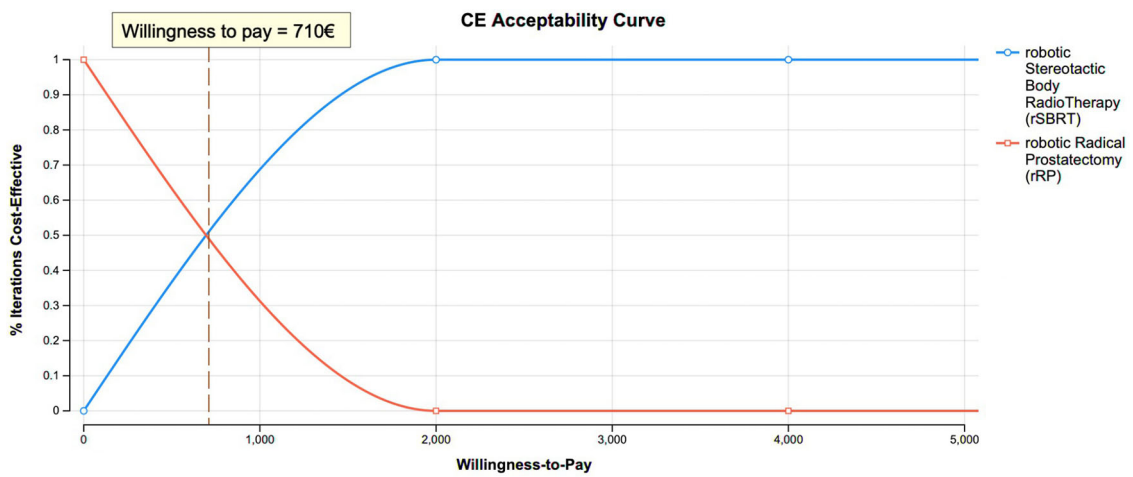

FIGURE 2 | Acceptability Curve (rRP vs rSBRT).

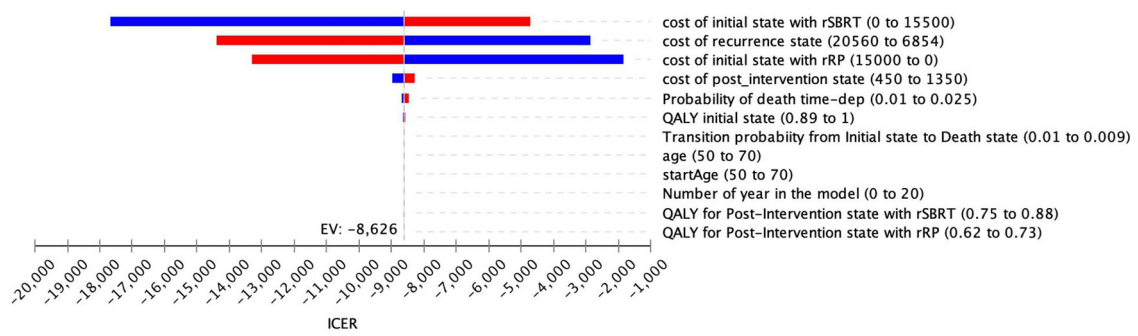

FIGURE 3 | Tornado diagram (rSBRT vs RP): One-way sensitivity analysis and variation of the ICER as a function of parameters listed.

rRP in previous studies, some studies focused the economic evaluation of rSBRT in comparison with intensity-modulated radiation therapy (IMRT) or proton therapy. In the United States, Sher et al. study concluded that robotic SBRT was more cost effective than conventional radiotherapy (IMRT) with an incremental cost-effectiveness ratio for conventional radiotherapy over robotic SBRT up to $285,000/QALY over a lifetime horizon for prostate cancer (7). Thus, rSBRT seems apparently less expensive but more toxic than conventional radiotherapy. In another American societal perspective, Parthan et al. evaluated that IMRT and proton therapy were both dominated by SBRT because they had higher costs and yielded fewer QALYs when compared with SBRT (ICERs: $9,991/-0.062 QALY for SBRT *vs* IMRT and $46,560/-0,047 QALY for SBRT *vs* PT) (23). In the Canadian societal perspective, Sharieff W et al. demonstrated that rSBRT was more cost-effective than standard treatments (including non-robotic SBRT) (24). When rSBRT was compared to the standard regimen using fixed-gantry system, the ICER was $2497/QALY for low-risk prostate cancer in Canada. Conversely, in the Czech healthcare system, rSBRT reached the same as/or lower ICER values than IMRT while the robotic SBRT acquisition cost was CZK 58 million lower. Therefore, IMRT was more cost-effective than rSBRT for localized prostate cancer treatment in Czech

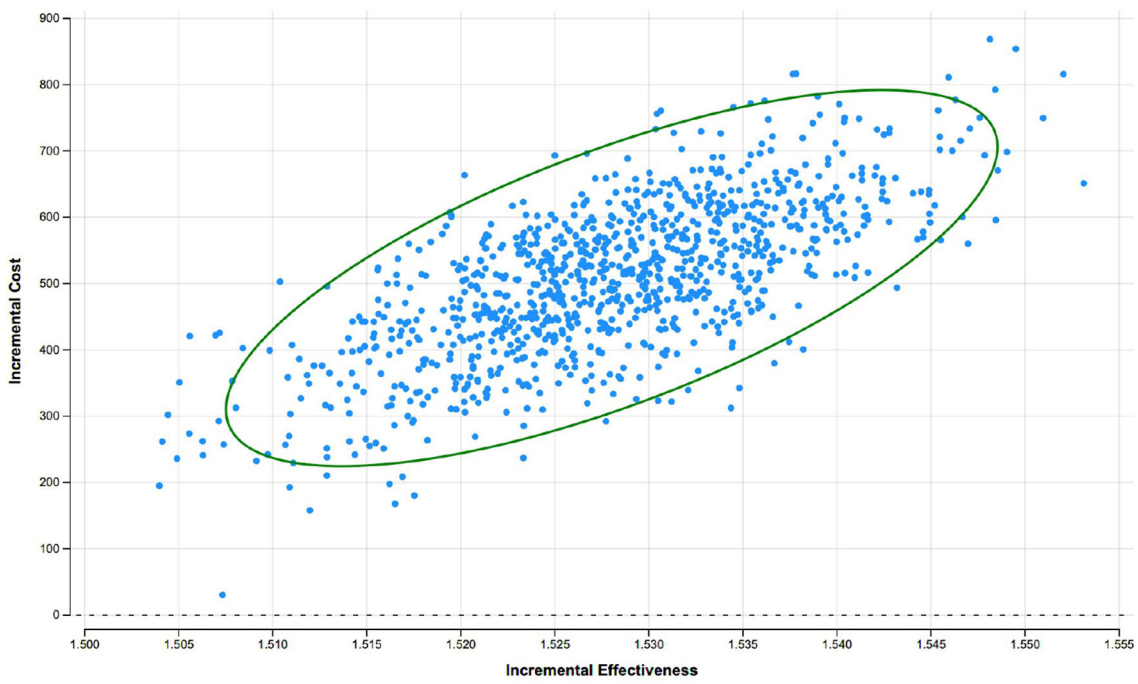

FIGURE 4 | Cost-effectiveness plane rSBRT vs. rRP at 10 years: results of the probabilistic sensitivity analysis with a Monte Carlo simulation showing the dispersion of 1000 ICER.

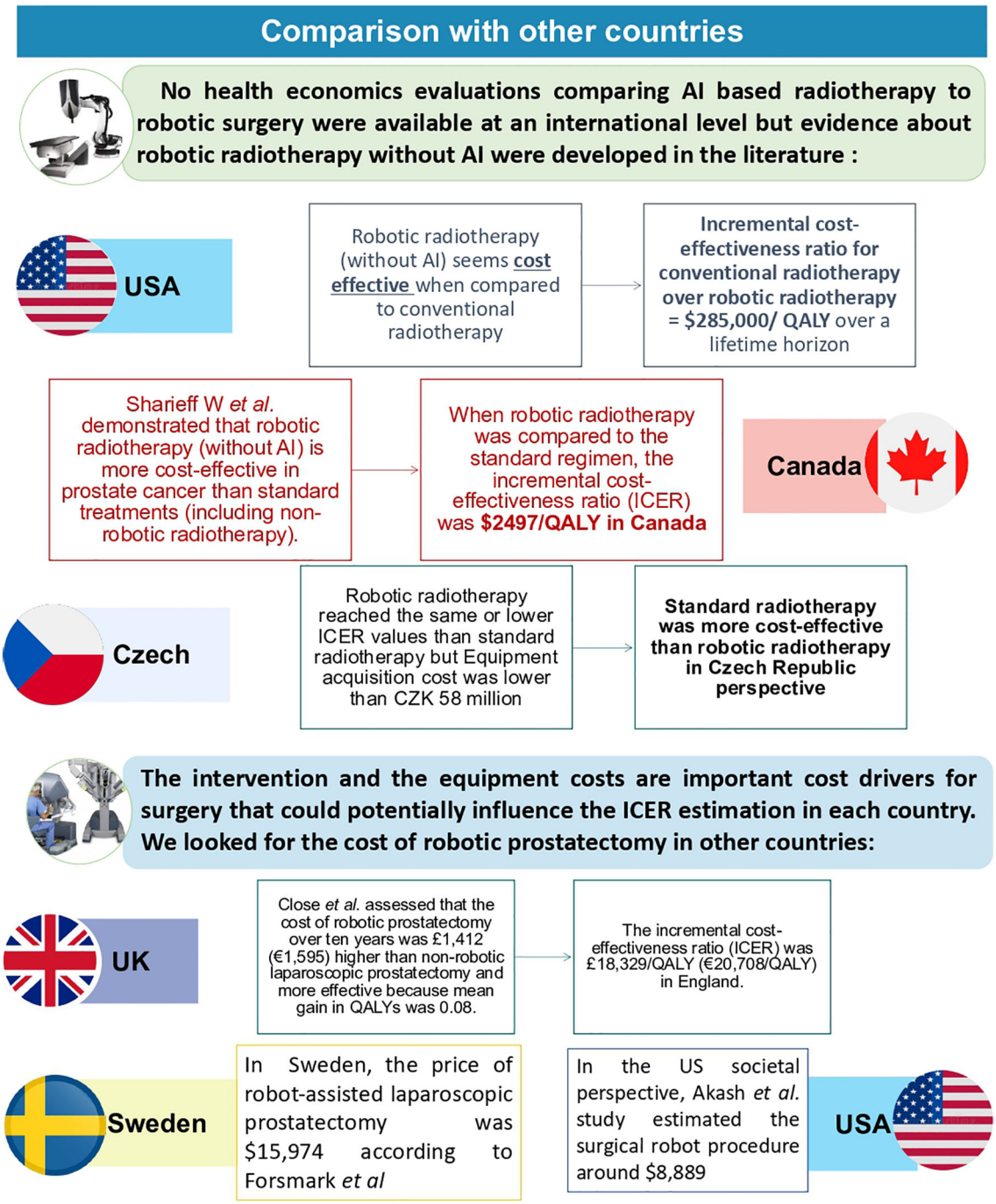

FIGURE 5 | Comparison of rRP and rSBRT evaluations in other countries.

Republic perspective (25). We summarize in **Figure 5** the different outcomes of the previous mentioned countries related to their different healthcare financing systems.

In addition, the intervention and equipment costs are important cost drivers for surgery and they could potentially influence the ICER estimation in each country. Therefore, we looked for the cost of robotic prostatectomy or their health economic evaluation in other countries. In the United Kingdom, Close et al. assessed that the cost of robotic prostatectomy over ten years was £1,412 (€1,595) higher than non-robotic laparoscopic prostatectomy and more effective because mean gain in quality of life years was 0.08 (26). The incremental cost-

effectiveness ratio (ICER) was £18,329/QALY (€20,708/QALY) in England. In the US societal perspective, Akash et al. estimated the surgical robot procedure around $8,889 (27). In Sweden, the price of robot-assisted laparoscopic prostatectomy was $15,974 according to Forsmark et al. (28). Finally, Perlbarg et al. literature review estimated the robot cost between €6,010 and €11,928 euros *per* patient in several countries (29). This difference suggested that further studies should be conducted in different countries in order to validate results.

However, to our knowledge, there have been no previous economic studies comparing robotic stereotactic radiotherapy/robot-assisted prostatectomy. In addition, we applied the recommendations of the French National Authority for Health to the model's fundamental assumptions (evaluation method, target population, time horizon and updates) (15). We selected a cost-utility approach to evaluate localized prostate cancer because our patients' 10-year life expectancy was the same as the 10-year life expectancy of same-age subjects from the general population. Thus, it is necessary to measure patients' quality of life rather than merely assess specific patients' survival end-points. We selected a 10-year follow-up period because a longer time frame would have unduly increased the degree of uncertainty of our results as clinical outcomes would not have been directly associated to any of the two interventions considered. A 10-year follow-up period permitted to evaluate the direct impact of the technique on patients' outcome; which is less applicable beyond the 10-year period. The utility data used was derived from the Katz et al. study that evaluated medium-term quality of life (5). This type of analysis has the added advantage of taking into account the one-year short-term period. Moreover, it permits to model the progressive evolution of patients' quality of life, 3 years after the intervention by integrating time-dependent QALY data.

As to costs, the cost of training of health care teams that, according to an interview conducted with experts (data not published), could amount to almost €800,000 in the case of rRP in public hospitals in Paris was not included. Costs of training staff for rSBRT should also be considered in the model but they are very difficult to document, as the Drummond et al. study showed (30). Training costs for rSBRT were not available this is why we could not integrate this parameter into our model. We based costs of the "recurrence" state on the Molinier et al. study (12). This estimate includes the costs of any secondary treatments within 5 years of the initial procedure and the total costs do not differ between the different disease risk levels (i.e., low, moderate or high risk). Since our current study exclusively focused on low-risk localized cancer cases, the assumptions based on the Molinier et al. study are expected to be conservative.

Our study includes several limitations. First, the absence of any prior study comparing rRP *versus* rSBRT in a French setting was problematic for the construction of our model. Indeed, it meant that we did not have any efficacy or quality of life data specific to French patients and further prospective studies about the French population are needed. Therefore, we assumed that the quality of life reported in the Katz et al. study for American patients would be similar for European ones. Secondly, our model did not consider a distal metastasis state since our target population consisted of low-risk patients followed up over a 10-year time horizon. Given the complexity of managing prostate cancer, we also had to simplify the treatment schedules in our model. We selected low-risk prostate cancer because the objective was to avoid adding confounding factors. If such analysis was chosen, we could not establish a direct correlation between the robot and its influence on costs or clinical results. Other variables could bias the analysis. Even if the two robotic techniques are among those that require higher financial investments because they are guided by robots, many therapeutic strategies in prostate cancer could be taken into account. Further health economic assessments such as Linac-based SBRT technology, for instance, could be particularly interesting. Finally, the active surveillance strategy initiated in patients whose cancer is not cured and who are classified in the "recurrence" state may potentially be confounded by additional psychological factors. We were unable to assess this impact from either a clinical or an economic perspective and therefore we omitted this state from the model. It would be interesting to consider an additional surveillance arm with real world data from further studies.

To conclude, there is an obvious lack of economic data to substantiate the additional costs and potential benefits of these different robot-assisted techniques. Thus, an economic evaluation comparing these new therapies, in particular robot-assisted radical prostatectomies and robot-assisted stereotactic body radiotherapy, would permit to estimate their benefits both for patients (at a clinical level) and for institutions (at an economical level). This would also provide a tool for financial-decision makers.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

LF, NMag, AT, NMar, IB, MZ, NS, TG, CC and OB contributed to the study conception and design. Material preparation, data collection and analysis were performed by LF, NMag, AT, NMar and IB. The first draft of the manuscript was written by LF, NMag, AT, NMar and IB. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.834023/full#supplementary-material

REFERENCES

1. INCA. *Le Cancer De La Prostate - Les Cancers Les Plus Fréquents*. Available at: https://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers/Les-cancers-les-plus-frequents/Cancer-de-la-prostate (Accessed July 17, 2019).
2. Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO, and AUA Evidence-Based Guideline. *Pract Radiat Oncol* (2018) 8:354–60. doi: 10.1016/j.prro.2018.08.002
3. Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Berg D. National Comprehensive Cancer Network Basal Cell and Squamous Cell Skin Cancers. Basal Cell and Squamous Cell Skin Cancers Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* (2004) 2(1):6–6. doi: 10.6004/jnccn.2004.0001
4. Herrell SD, Smith JA. Robotic-Assisted Laparoscopic Prostatectomy: What is the Learning Curve? *Urology* (2005) 66:105–7. doi: 10.1016/j.urology.2005.06.084
5. Katz A. Stereotactic Body Radiotherapy for Low-Risk Prostate Cancer: A Ten-Year Analysis. *Cureus* (2017) 9(9):e1668. doi: 10.7759/cureus.1668
6. Katz AJ, Santoro M, Ashley R, Diblasio F, Witten M. Stereotactic Body Radiotherapy for Organ-Confined Prostate Cancer. *BMC Urol* (2010) 10:1. doi: 10.1186/1471-2490-10-1
7. Sher DJ, Parikh RB, Mays-Jackson S, Punglia RS. Cost-Effectiveness Analysis of SBRT Versus IMRT for Low-Risk Prostate Cancer. *Am J Clin Oncol* (2014) 37:215–21. doi: 10.1097/COC.0b013e31827a7d2a
8. AMELI. *Améliorer La Qualité Du Système De Santé Et Maîtriser Les Dépenses - Propositions De L'assurance Maladie Pour 2020* (2019). Available at: https://www.ameli.fr/fileadmin/user_upload/documents/190701_CP20_rapport_Vdef_complete.pdf?fbclid=IwAR2NnKoFnnJvbwkEMmJka1RbNGQ06W0cwGgV2Q3fXK28n1tBxqdiEYes-ao (Accessed July 9, 2019).
9. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value Health* (2013) 16:231–50. doi: 10.1016/j.jval.2013.02.002
10. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity-Modulated Fractionated Radiotherapy Versus Stereotactic Body Radiotherapy for Prostate Cancer (PACE-B): Acute Toxicity Findings From an International, Randomised, Open-Label, Phase 3, non-Inferiority Trial. *Lancet Oncol* (2019) 20:1531–43. doi: 10.1016/S1470-2045(19)30569-8
11. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-Reported Outcomes After Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med* (2016) 375:1425–37. doi: 10.1056/NEJMoa1606221
12. Molinier L, Castelli C, Bauvin E, Rebillard X, Soulié M, Daurès J-P, et al. Cost Study of the Clinical Management of Prostate Cancer in France: Results on the Basis of Population-Based Data. *Eur J Health Econ HEPAC Health Econ Prev Care* (2011) 12:363–71. doi: 10.1007/s10198-010-0250-6
13. Sanyal C, Aprikian A, Cury F, Chevalier S, Dragomir A. Clinical Management and Burden of Prostate Cancer: A Markov Monte Carlo Model. *PLoS One* (2014) 9:e113432. doi: 10.1371/journal.pone.0113432
14. INSEE. *Tables De Mortalité Par Sexe, Âge Et Niveau De Vie – Tables De Mortalité Par Niveau De Vie | Insee*. Available at: https://www.insee.fr/fr/statistiques/3311422?sommaire=3311425 (Accessed August 6, 2019).
15. Haute Autorité de santé. *Guide Méthodologique - Choix Méthodologiques Pour L'évaluation Économique À La HAS* (2011). Available at: https://www.has-sante.fr/upload/docs/application/pdf/2011-11/guide_methodo_vf.pdf (Accessed February 12, 2019).
16. AMELI. *Tarifs Des Consultations Françaises*. Available at: https://www.ameli.fr/assure/remboursements/rembourse/consultations/modifications-tarifs-consultations-mai-2017 (Accessed July 26, 2019).
17. ENC MCO. *Stats ATIH* . Available at: https://www.scansante.fr/applications/enc-mco/submit?snatnav=&annee=2016&secteur=oqn&type_activite=ghs&cmd=&souscmd=&racine=11C10&ghm=11C10&mbout=dummy&num_selection=11C10&type_selection=racine&zip=non.%20Accessed%20August%2026,%202019 (Accessed February 5, 2022).
18. Scotte F, Martelli N, Vainchtock A, Borget I. The Cost of Thromboembolic Events in Hospitalized Patients With Breast or Prostate Cancer in France. *Adv Ther* (2015) 32:138–47. doi: 10.1007/s12325-015-0187-3
19. Haute Autorité de santé. *Rapport D'évaluation Technologique : Évaluation Des Dimensions Clinique Et Organisationnelle De La Chirurgie Robot-Assistée Dans Le Cadre D'une Prostatectomie Totale*, Vol. 255. Saint-Denis, France: Haute Autorité de Santé (2016).
20. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-Assisted Laparoscopic Prostatectomy Versus Open Radical Retropubic Prostatectomy: Early Outcomes From a Randomised Controlled Phase 3 Study. *Lancet* (2016) 388:1057–66. doi: 10.1016/S0140-6736(16)30592-X
21. Wallerstedt A, Tyritzis SI, Thorsteinsdottir T, Carlsson S, Stranne J, Gustafsson O, et al. Short-Term Results After Robot-Assisted Laparoscopic Radical Prostatectomy Compared to Open Radical Prostatectomy. *Eur Urol* (2015) 67:660–70. doi: 10.1016/j.eururo.2014.09.036
22. Health Quality Ontario. Robotic Surgical System for Radical Prostatectomy: A Health Technology Assessment. *Ont Health Technol Assess Ser* (2017) 17:1–172.
23. Parthan A, Pruttivarasin N, Davies D, Taylor DCA, Pawar V, Bijlani A, et al. Comparative Cost-Effectiveness of Stereotactic Body Radiation Therapy Versus Intensity-Modulated and Proton Radiation Therapy for Localized Prostate Cancer. *Front Oncol* (2012) 2:81. doi: 10.3389/fonc.2012.00081
24. Sharieff W, Greenspoon JN, Dayes I, Chow T, Wright J, Lukka H. The Technique, Resources and Costs of Stereotactic Body Radiotherapy of Prostate Cancer: A Comparison of Dose Regimens and Delivery Systems. *Technol Cancer Res Treat* (2016) 15:171–8. doi: 10.7785/tcrt.2012.500431
25. Horáková D, Donin G. Economic Evaluation of Robotic Radiosurgery System for Prostate Cancer Treatments in the Czech Republic. In: L Lhotska, L Sukupova, I Lacković, GS Ibbott, editors. *World Congress on Medical Physics and Biomedical Engineering 2018*. Singapore: Springer Singapore (2019). p. 113–8. doi: 10.1007/978-981-10-9038-7_20
26. Close A, Robertson C, Rushton S, Shirley M, Vale L, Ramsay C, et al. Comparative Cost-Effectiveness of Robot-Assisted and Standard Laparoscopic Prostatectomy as Alternatives to Open Radical Prostatectomy for Treatment of Men With Localised Prostate Cancer: A Health Technology Assessment From the Perspective of the UK National Health Service. *Eur Urol* (2013) 64:361–9. doi: 10.1016/j.eururo.2013.02.040
27. Bijlani A, Hebert AE, Davitian M, May H, Speers M, Leung R, et al. A Multidimensional Analysis of Prostate Surgery Costs in the United States: Robotic-Assisted Versus Retropubic Radical Prostatectomy. *Value Health* (2016) 19:391–403. doi: 10.1016/j.jval.2015.12.019
28. Forsmark A, Gehrman J, Angenete E, Bjartell A, Björholt I, Carlsson S, et al. Health Economic Analysis of Open and Robot-Assisted Laparoscopic Surgery for Prostate Cancer Within the Prospective Multicentre LAPPRO Trial. *Eur Urol* (2018) 74:816–24. doi: 10.1016/j.eururo.2018.07.038
29. Perlbarg J, Rabetrano H, Soulié M, Salomon L, Durand-Zaleski I. Évaluation Médico-Économique De La Chirurgie Et Des Autres Primo-Traitements Du Cancer De La Prostate non Métastatique. *Prog Urol* (2015) 25:1108–15. doi: 10.1016/j.purol.2015.07.012
30. Drummond M, Tarricone R, Torbica A. "Economic Evaluation of Medical Devices". In: *Oxford Research Encyclopedia of Economics and Finance*. Oxford, United Kingdom:Oxford University Press (2018). doi: 10.1093/acrefore/9780190625979.013.105

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 07 June 2022
doi: 10.3389/fonc.2022.898774

Risk Factors for Biochemical Recurrence After PSMA-PET-Guided Definitive Radiotherapy in Patients With *De Novo* Lymph Node-Positive Prostate Cancer

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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: 17 March 2022
Accepted: 02 May 2022
Published: 07 June 2022

Citation:
Spohn SKB, Birkenmaier V, Ruf J, Mix M, Sigle A, Haehl E, Adebahr S, Sprave T, Gkika E, Rühle A, Nicolay NH, Kirste S, Grosu AL and Zamboglou C (2022) Risk Factors for Biochemical Recurrence After PSMA-PET-Guided Definitive Radiotherapy in Patients With De Novo Lymph Node-Positive Prostate Cancer. Front. Oncol. 12:898774. doi: 10.3389/fonc.2022.898774

Introduction: The National Comprehensive Cancer Network recommends external beam radiotherapy (EBRT) combined with androgen deprivation therapy (ADT) as the preferred treatment option for newly diagnosed node-positive (cN1) prostate cancer (PCa) patients. However, implementation of positron emission tomography targeting prostate-specific membrane antigen (PSMA-PET) in the staging of primary PCa patients has a significant impact on RT treatment concepts. This study aims to evaluate outcomes and their respective risk factors on patients with PSMA-PET-based cN1 and/or cM1a PCa receiving primary RT and ADT.

Methods: Forty-eight patients with cN0 and/or cM1a PCa staged by [^{18}F]PSMA-1007-PET (n = 19) or [^{68}Ga]PSMA-11-PET (n = 29) were retrospectively included. All patients received EBRT to the pelvis ± boost to positive nodes, followed by boost to the prostate. The impact of different PET-derived characteristics such as maximum standard uptake value (SUVmax) and number of PET-positive lymph nodes on biochemical recurrence-free survival (BRFS) (Phoenix criteria) and metastasis-free survival (MFS) was determined using Kaplan–Meier and Cox proportional hazard regression analyses.

Results: Median follow-up was 24 months. Median initial serum prostate-specific antigen was 20.2 ng/ml (IQR 10.2–54.2). Most patients had cT stage ≥ 3 (63%) and ISUP grade ≥ 3 (85%). Median dose to the prostate, elective nodes, and PET-positive nodes was 75 Gy, 45 Gy, and 55 Gy, respectively. Ninety percent of patients received ADT with a median duration of 9 months (IQR 6–18). In univariate analysis, cM1a stage (p = 0.03), number of >2 pelvic nodes (p = 0.01), number of >1 abdominal node (p = 0.02), and SUVmax values ≥ median (8.1 g/ml for ^{68}Ga-PSMA-11 and 7.9 g/ml for ^{18}F-PSMA-1007) extracted from lymph nodes were

significantly associated with unfavorable BRFS, but classical clinicopathological features were not. Number of >2 pelvic nodes (n = 0.03), number of >1 abdominal node (p = 0.03), and SUVmax values ≥ median extracted from lymph nodes were associated with unfavorable MFS. In multivariate analysis, number of >2 pelvic lymph nodes was significantly associated with unfavorable BRFS (HR 5.2, p = 0.01) and SUVmax values ≥ median extracted from lymph nodes had unfavorable MFS (HR 6.3, p = 0.02).

Conclusion: More than 2 PET-positive pelvic lymph nodes are associated with unfavorable BRFS, and high SUVmax values are associated with unfavorable MFS. Thus, the number of PET-positive lymph nodes and the SUVmax value might be relevant prognosticators to identify patients with favorable outcomes.

Keywords: risk factors, PSMA-PET/CT, prostate cancer, radiotherapy, personalization, lymph node positive

INTRODUCTION

Node-positive prostate cancer represents approximately 12% of *de novo* diagnosed prostate cancer (PCa) in the United States based on conventional imaging. Current National Comprehensive Cancer Network (NCCN v3.2022) guidelines recommend androgen deprivation therapy (ADT) with radiotherapy (RT) to the prostate and pelvic lymphatics in case of *de novo* pelvic lymph-node positive PCa (cN1 stage). ADT can be accompanied by abiraterone due to the recently reported benefit in metastasis-free survival (MFS) in this patient group in the STAMPEDE platform trial (1). In case of lymph node metastases above the aortic bifurcation (cM1a stage), current guidelines (NCCN v3.2022) recommend ADT with next-generation antiandrogens or doxetacel. In selected patients, RT to the prostate can be offered in addition to systemic therapy (2). Current risk-classification systems for these patient groups consider the localization of lymph node metastases (cN1 vs. cM1a stage). However, the number of affected lymph nodes and their biologic characteristics are not considered.

It is important to mention that all latter treatment recommendations and risk-classification systems are based on studies using conventional imaging for staging: computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy. The proPSMA study compared prostate-specific membrane antigen positron emission tomography (PSMA-PET) with conventional imaging for staging in high-risk PCa patients (3). Twenty-nine percent of patients undergoing first-line PSMA-PET were detected with pelvic nodal (20%) or abdominal nodal (9%) metastases (3). The authors depicted a significantly higher sensitivity and accuracy for PSMA-PET in the detection of lymph node metastases. Clinical trials correlating PSMA-PET-positive findings with histopathology from pelvic lymph node dissection in intermediate- to high-risk PCa patients showed somewhat poorer performance on a region level with a sensitivity between 40% and 66% and a specificity between 95% and 98% (4, 5). Several studies observed a significant impact of PSMA-PET imaging on RT treatment concepts in patients with primary PCa (6, 7). However, reports on the outcome after PSMA-PET-guided RT in PCa patients with *de novo* metastasized lymph nodes are sparse. Thus, we initiated this retrospective study in order to (i) evaluate the biochemical recurrence-free survival and (ii) its respective risk factors in a cohort of patients with initial cN1 and/or cM1a PCa receiving primary RT and ADT after PSMAPET staging.

PATIENTS AND METHODS

Patients

This retrospective, mono-institutional analysis included patients with histologically proven PCa and cN1 and/or cM1a status in initial PSMA-PET/CT imaging. All patients received intensity-modulated RT (IMRT) with or without ADT from July 2015 to March 2021. The availability of PSMA-PET/CT scans at the maximum of 6 months prior to IMRT was mandatory. Patients were excluded from the analysis if not all PET-positive lymph nodes were included in the RT field or had cM1b/c disease (bone and/or visceral metastases) in PET. This study was approved by the institutional review board of the University of Freiburg (No.: 21-1149) and written informed consent was waived due to the retrospective character.

PSMA-PET/CT Imaging

Radiolabeled tracers targeting the PSMA have been used for detection and delineation of lymph node metastases. PET/CT scans were performed 1 or 2 h after injection of the ligand ^{68}Ga-PSMA-11 (n = 29) or ^{18}F-PSMA-1007 (n = 19), respectively. The imaging systems used were GEMINI TF TOF 64, GEMINI TF 16 Big Bore, and Vereos (all from Philips, Netherlands). All imaging systems were cross-calibrated. A detailed description of our PSMA PET/CT imaging protocol is given in (8, 9).

Treatment Protocol

Planning CT was acquired in supine position. Clinical target volume (CTV) and planning target volume (PTV) were created according to NRG and ACROP-ESTRO recommendations (10, 11). In all patients, the RT field comprised the prostate, the seminal vesicles, and the pelvic lymph nodes. In case of cN1

status, the upper border of the CTV was the aortic bifurcation. In case of cM1a status, the upper border of the CTV was 1 cm above the last PET-positive lymph node including elective pelvic nodes. Co-registered PET images were used to identify positive lymph nodes in the planning CT under consideration of the local nuclear medicine report and any SUV uptake higher than the background. PTV margin for boost volumes of PET-positive nodes was 1 cm. All patients received normo-fractionated IMRT and image-guided RT (IGRT). In the first step, RT was applied to the prostate, seminal vesicles, and elective lymphatics including a boost to PET-positive lymph nodes. In the second step, the prostate and the seminal vesicles received a sequential boost.

The aimed prescription dose was 76 Gy (EQD2, $\alpha/\beta = 1.6$ Gy) to the entire prostatic gland and one-third of the seminal vesicles. No RT dose escalation to intraprostatic volumes was performed. Elective pelvic and abdominal lymphatics received 45–50.4 Gy in 1.8 Gy per fraction. Similar to (12), the aimed prescription dose for PET-positive lymph nodes was 54 Gy (EQD2, $\alpha/\beta = 1.6$ Gy).

Administration of ADT was performed under consideration of patients' individual preferences and comorbidities. Long-time ADT was strongly recommended to all patients concomitantly and adjuvant to EBRT. Neoadjvuant ADT was recommended if shrinkage of prostate volume was intended.

During follow-up (FU), patients were seen every 3–6 months for the first 2 years and every 6–12 months thereafter for physical examination and PSA measurements. FU examinations were performed at our institution or from another board-licensed urologist. Genitourinary (GU) and gastrointestinal (GI) toxicities were assessed according to common terminology criteria for adverse events (CTCAE) v5.0. Radiologic evaluation by PSMA-PET/CT was conducted in case of biochemical recurrence according to Phoenix criteria (13). In case of oligoprogression, metastasis-directed therapy (MDT) was offered to patients.

Standardized-Uptake Value Analysis

All PET-positive lymph nodes were contoured by SS, applying validated contouring techniques (8, 9) under consideration of the local PET review and the anatomical borders on the corresponding CT scan in Eclipse planning treatment software 15.0 (Varian, USA). Subsequently, maximum standardized uptake values (SUVmax) were extracted from the prostate and lymph nodes.

Statistical Analysis

The primary endpoint biochemical recurrence-free survival (BRFS) was defined as time from completion of IMRT until biochemical recurrent PCa according to the Phoenix criteria (13) or death from any cause. MFS was calculated from completion of RT until detection of any new metastases outside the RT field on PSMA-PET or death from any cause. Uni- and multivariate (forward logistic regression) Cox regression analyses were performed analyzing the impact of different clinical variables on BRFS. Therefore, variables were dichotomized: initial serum prostate-specific antigen (iPSA) ≤ and > 20 ng/ml, International Society for Urological Pathology (ISUP) grade < and ≥ 3, T-stage < and ≥ 3, cM1a stage, number of positive pelvic lymph nodes ≤ and > 2, and number of extrapelvic lymph nodes ≤ and > 1. SUVmax values within the prostate and within the PET-positive lymph nodes were dichotomized according to median values, respectively. To account for differences in SUVmax between ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007, the median was calculated for each tracer separately. For the graphical representation, the respective variables were analyzed by Kaplan–Meier survival curve compared by log-rank test. Mann–Whitney test and Wilcoxon matched-pairs signed rank test was used for *t*-test of unpaired and paired data. All tests were considered to be statistically significant at $p < 0.05$. Statistical analysis was conducted with SPSS v28 (IBM, USA). Descriptive statistics were performed with Excel 2016 (Microsoft Cooperation, USA) and GraphPad Prism v8.4.2 (GraphPad Software Inc, USA).

RESULTS

Patient and Treatment Characteristics

Forty-eight patients with a median FU of 23 months (IQR 8–38 months) were included. See **Table 1** for patient characteristics. Twenty-nine patients underwent ^{68}Ga-PSMA-11-PET and 19 patients underwent ^{18}F-PSMA-1007-PET. cN1 stage was significantly different when considering CT scans only ($p < 0.0001$), whereas cM1a stage was not ($p = 0.25$). Median dose to the prostate, PET-positive lymph nodes, and elective nodes were 75 Gy, 55 Gy, and 45 Gy. Median SUVmax of the prostate and lymph nodes was 17.8 g/ml (IQR 9.9–28.9) and 8.1 g/ml (IQR 4.1–23.0) for ^{68}Ga-PSMA-11 and 17.3 g/ml (IQR 9.3–31.9) and 7.9 g/ml (IQR 4.4–18.3) for ^{18}F-PSMA-1007, respectively. Only one patient had PSMA-PET positive lymph nodes above the diaphragm. Cumulative acute grade 1 and 2 GI toxicities were 33% and 19%, and acute GU toxicities were 60% and 23%. Cumulative chronic grade 1 and 2 GI toxicities were 13% and 4%, and chronic GU toxicities were 13% and 6%. There was no significant difference of acute and chronic GU and GI toxicities between patients with and without cM1a stage ($p > 0.11$). No chronic grade 3 toxicities were observed.

During FU, 17 patients (35%) experienced a biochemical relapse. Eight patients were diagnosed with metastases in PSMA-PET/CT due to relapse, of which metastases were outside the RT field in 7 patients. Two-year and 4-year BRFS were 69% and 52%, respectively. Two-year and 4-year MFS were 75% and 52%, respectively.

In univariate analysis, presence of cM1a stage ($p = 0.03$), >2 pelvic lymph nodes ($p = 0.01$), and >1 abdominal lymph node ($p = 0.02$) were associated with unfavorable BRFS, whereas the established clinical and pathological parameters were not (see **Table 2**). Additionally, SUVmax values ≥ median extracted from the prostate were not associated with BRFS ($p = 0.89$), while SUVmax values ≥ median extracted from lymph nodes were associated with unfavorable BRFS ($p = 0.046$). In multivariate analysis, only number of pelvic lymph nodes > 2 remained statistically significant ($p = 0.01$). In univariate analysis, presence of >2 pelvic lymph nodes ($p = 0.03$), >1 abdominal lymph node ($p = 0.03$), and SUVmax values ≥ median extracted from lymph nodes were associated with unfavorable MFS, while cM1a stage and

TABLE 1 | Patient characteristics.

Median age in years (range)	75 (58–86)
Median initial PSA in ng/ml (IQR)	20.2 (10.2–54.2)
ISUP grade	n (%)
1	0 (0)
2	5 (10)
3	16 (33)
4	12 (25)
5	13 (27)
n/a	2 (4)
cT stage	*n* (%)
1–2	12 (25)
3a	12 (25)
3b	18 (38)
4	6 (12)
cN1 stage according to PSMA-PET/CT	48 (100)
cN1 stage according to CT	32 (66)
cM1a stage according to PSMA-PET/CT	12 (25)
cM1a stage according to CT	10 (21)
Number of PSMA-PET positive pelvic lymph nodes	Median and IQR = 2 (1–4)
	n (%)
1	16 (33)
2	10 (21)
3	9 (19)
4	5 (10)
5	3 (6)
6	5 (10)
Number of PSMA-PET positive abdominal lymph nodes	*n* (%)
0	38 (79)
1	4 (11)
2	2 (4)
3	3 (6)
4	1 (2)
ADT	*n* (%)
Yes	43 (90)
No	5 (10)
Median duration of ADT in months (IQR)	9 (6–18)
Median PSA nadir (IQR)	0.17 (0.1–0.7)

PSA, prostate specific antigen; IQR, interquartile range; ISUP grade, International Society of Urologic Pathology grade; PSMA-PET, positron emission tomography targeting prostate-specific membrane antigen; ADT, androgen deprivation therapy.

clinicopathological parameters were not (see **Table 2**). In multivariate analysis, only SUVmax values ≥ median extracted from lymph nodes remained statistically significant regarding MFS ($p = 0.02$). See **Table 2** for details and **Figure 1** for Kaplan–Meier curves.

DISCUSSION

To the best of our knowledge, this is one of the first studies to analyze treatment outcomes after RT in PCa patients with cN1 and/or cM1a status on initial PSMA-PET/CT. Despite prior clinical implementation of PSMA-PET, *de novo* lymph node-positive PCa has been scarcely investigated in clinical trials. Addition of RT to ADT has been proven to improve outcomes (14), but the utilization of PSMA-PET in primary staging leads to subsequent stage migration due to the increased detection rate of node and bone metastases. This, in addition to modern RT techniques, bears the potential to adjust and improve the management of node-positive PCa.

In our cohort, 4-year BRFS was worse than the results of a retrospective study (15) investigating moderately hypofractionated RT in node-positive PCa patients. All patients in this study received long-term ADT, and patients in our cohort had more advanced disease with >75% having cT3–4 stage, which might account for these differences. Despite a slightly different definition of BCR (namely, PSA > 1.5 ng/ml), results of the RTOG 8531 trial are in a more similar range with a 5-year BCFS of 54% in patients receiving RT + ADT (14). The recently published data from the STAMPEDE platform (1) demonstrate that outcomes can be significantly improved through intensification of systemic treatments by adding abiraterone to long-term ADT. Despite our cohort consisting of high-risk PCa patients with mainly cT3b and node-positive disease, duration of ADT was remarkably lower, which might be responsible for the poorer BRFS rates. Low rates of ADT might be attributed to patients' preferences and comorbidities. However, improved outcomes through intensive

TABLE 2 | Univariate and multivariate Cox regression. *p*-values and hazard ratio (HR) with 95% confidence interval (CI) are shown for biochemical recurrence-free survival (BRFS) and metastasis-free survival (MFS).

Univariate analysis	**BRFS**		**MFS**	
	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95%CI)**
Initial PSA	0.83	1.1 (0.4–3.2)	0.89	0.9 (0.3–3.0)
ISUP	0.94	1.1 (0.1–8.5)	0.69	0.7 (0.1–5.3)
cT stage	0.53	1.5 (0.4–5.4)	0.37	2.0 (0.4–9.5)
cM1a stage	**0.03**	3.7 (1.2–11.9)	0.24	2.3 (0.6–9.3)
>2 pelvic lymph nodes	**0.01**	5.2 (1.4–18.9)	**0.03**	5.7 (1.2–26.7)
>1 abdominal lymph node	**0.02**	4.3 (1.3–14.5)	**0.03**	4.6 (1.1–18.5)
SUVmax ≥ median in prostate	0.89	0.9 (0.3–2.6)	0.29	0.5 (0.1–1.8)
SUVmax ≥ median in lymph nodes	**0.046**	3.26 (1.02–10.4)	**0.02**	6.3 (1.4–29.2)
Multivariate analysis				
cM1a stage	ns			
>2 pelvic lymph nodes	**0.01**	5.2 (1.4–18.9)	ns	
>1 abdominal lymph node	ns		ns	
SUVmax ≥ median in lymph nodes	ns		**0.02**	6.3 (1.4–29.2)

PSA, prostate-specific antigen; ISUP, International Society of Urologic Pathology grade; cT stage, clinical tumor stage; cM1a, presence of extrapelvic lymph nodes; SUVmax, maximum standard uptake value; ns, non-significant. Statistical significant p-values are shown in bold.

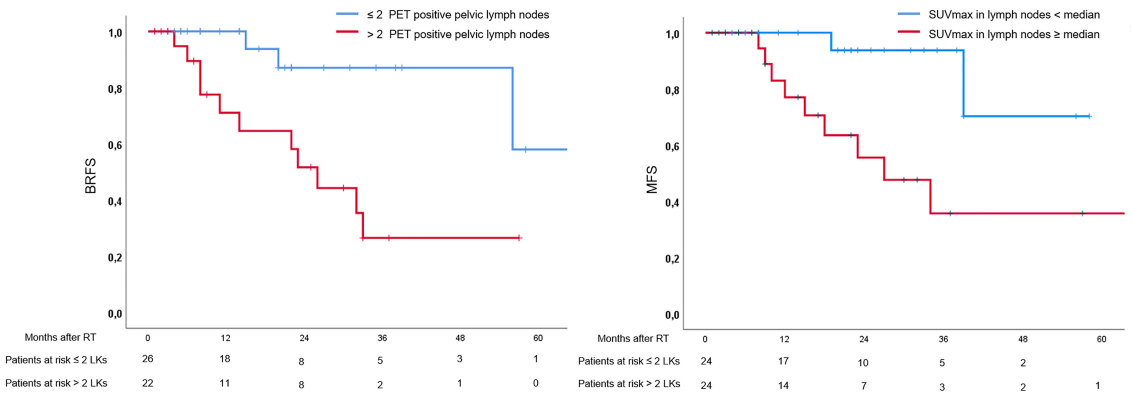

FIGURE 1 | Kaplan–Meier curves. Left: Curves for biochemical recurrence-free survival in patients with > and ≤ 2 positive lymph nodes in positron emission tomography (PET). Right: Curves for metastasis-free survival (MFS) in patients with maximal standardized uptake values (SUVmax) ≥ and < median.

systemic therapies come at the costs of adverse effects and financial burden. Consequently, further prognosticators are needed to identify patients who are at lower risk of relapse and thus would putatively benefit from intensified local therapies rather than systemic treatments. In this regard, our results demonstrate that RT achieves high local control rates, since only patients experienced in-field nodal recurrence.

In our analysis, established clinical and pathology parameters were not statically significantly associated with BRFS or MFS. This observation has also been previously described in studies investigating patients with PCa recurrence and reflects the putative clinical relevance of PSMA-PET-positive findings (16). These results suggest the hypothesis that patients with nodal spread diagnosed with PSMA-PET are at higher risk irrespective of the tumor extension and histopathology of the primary tumour. These established risk factors are particularly validated in localized PCa, but might be less relevant in patients with metastases. Presence of cM1a stage was statistically significant in univariate analysis, but only number of >2 positive pelvic lymph nodes remained significant in multivariate analysis. These results suggest that in the PSMA-PET era, the number of PET-positive pelvic lymph nodes might be a relevant prognosticator in patients with node-positive PCa undergoing RT + ADT. The prognostic role of the number of positive lymph nodes has been previously described by Briganti et al., who demonstrated that after radical prostatectomy and extended pelvic lymph node dissection, patients with ≤2 positive nodes experience improved cancer-specific survival compared to patients with >2 lymph nodes (17). Interestingly, we found the same cutoff for PSMA-PET-positive lymph nodes. Possibly, the historical differentiation between patients with pelvic and extrapelvic lymph node metastases might be less relevant than the tumor burden detected by PSMA-PET. Larger studies are warranted to confirm these results and investigate the role of extrapelvic nodal PSMA-positive spread. Nevertheless, these findings suggest that quantification of tumor burden is a potential tool to identify candidates who benefit from local treatments rather than from intensified systemic treatment. Local RT can be delivered to elective nodes or as part of an MDT. Elective nodal irradiation has been shown to improve outcomes compared to MDT in nodal oligorecurrence after surgery at the cost of toxicities (18). However, late toxicities were low in our cohort of patients who did not receive any prior treatment. Whether the optimal local treatment consists of irradiation of elective nodes or MDT in the setting of extended nodal spread needs to be assessed in future studies.

In addition to improved metastasis detection, PSMA-PET comprises biological information as it is using molecular tracers. It has been demonstrated that expression of PSMA correlates with worse GS and lymph node involvement in prostatectomy specimens and is associated with worse outcomes (19, 20). Since SUVmax correlates with PSMA expression (21), its analysis might enable to identity prognostic imaging biomarkers. We considered median SUVmax values for ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 separately, since both tracers obtain different PSMA updates. In our exploratory analysis, SUVmax values ≥ median extracted from lymph nodes were associated with unfavorable BRFS, potentially representing patients with biologically more aggressive disease. Radiomic features (RFs) allow extracting deeper information from medical images (22), enabling non-invasive tumor characterization and prediction of lymph node involvement (23). Thus, image analysis through RF bears the potential to identify additional prognosticators and should be analyzed in the future. Interestingly, SUVmax values were the only significant parameter for MFS in multivariate analysis. These results suggest the hypothesis, that SUVmax might be a potential predictor to identify patients who are at higher risk for systemic progress, whereas patients with BRFS might suffer from in-field and out-of-field recurrence. The relatively low number of patients should be considered for interpretation of this statistical analysis. However, these interesting results need to be evaluated in larger cohorts with longer FU.

There are several limitations to our study. First, due to its retrospective character, PSMA-PET/CT, RT, and FU protocols were not consistent within all patients. Most notably, two different PSMA tracers were used. However, a study by Kuten et al. showed only small differences between both tracers by using histopathology as standard of reference (24). Second, no

central review of PET imaging findings was performed. Thus, it is likely to have an ascertainment bias in the diagnosis of lymph nodes. Third, 5 patients in our study rejected the admission of ADT, and the median duration of ADT was only 9 months. Since it is unclear whether the inclusion of all PET-positive lesion into the RT field may allow a reduction of ADT, our study cohort had a possible undertreatment regarding systemic therapies. Finally, the FU time in our study is relatively short and the patient number is limited. Nevertheless, we believe that our study provides important results on RT of PET-positive lymph nodes, and the results should be evaluated in larger and preferably prospectively collected patient cohorts.

CONCLUSION

Our results support the need for a more sophisticated differentiation of patients with *de novo* node-positive PCa. The number of PET-positive lymph nodes and the SUVmax value might be relevant prognosticators to identify patients with favorable outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the University of Freiburg. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SS and CZ contributed to the conception and design of the study. SS and VB collected data. SS concducted the statistical analysis. JR and MM were responsible for the conduction and reporting of the PSMA-PET/CTs. AS was involved in ADT treatment. EH, SA, TS, EG, AR, and SK were involved in radiotherapy treatment. NN and AG supervised the study. SS wrote the first draft of the manuscript. CZ wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the German Federal Ministry for Education and Research (BMBF JTC 2018 01KU1913) as part of the PersoProCaRisk grant.

REFERENCES

1. Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, Parker CC, et al. Abiraterone Acetate and Prednisolone With or Without Enzalutamide for High-Risk non-Metastatic Prostate Cancer: A Meta-Analysis of Primary Results From Two Randomised Controlled Phase 3 Trials of the STAMPEDE Platform Protocol. *Lancet* (2022) 399(10323):447–60. doi: 10.1016/S0140-6736(21)02437-5
2. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): A Randomised Controlled Phase 3 Trial. *Lancet* (2018) 392(10162):2353–66. doi: 10.1016/S0140-6736(18)32486-3
3. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-Specific Membrane Antigen PET-CT in Patients With High-Risk Prostate Cancer Before Curative-Intent Surgery or Radiotherapy (proPSMA): A Prospective, Randomised, Multicentre Study. *Lancet* (2020) 395 (10231):1208–16. doi: 10.1016/S0140-6736(20)30314-7
4. Hope TA, Eiber M, Armstrong WR, Juarez R, Murthy V, Lawhn-Heath C, et al. Diagnostic Accuracy of 68Ga-PSMA-11 PET for Pelvic Nodal Metastasis Detection Prior to Radical Prostatectomy and Pelvic Lymph Node Dissection: A Multicenter Prospective Phase 3 Imaging Trial. *JAMA Oncol* (2021) 7 (11):1635–42. doi: 10.1001/jamaoncol.2021.3771
5. Gorin MA, Rowe SP, Patel HD, Vidal I, Mana-Ay M, Javadi MS, et al. Prostate Specific Membrane Antigen Targeted (18)F-DCFPyL Positron Emission Tomography/Computerized Tomography for the Preoperative Staging of High Risk Prostate Cancer: Results of a Prospective, Phase II, Single Center Study. *J Urol* (2018) 199(1):126–32. doi: 10.1016/j.juro.2017.07.070
6. Schmidt-Hegemann NS, Eze C, Li M, Rogowski P, Schaefer C, Stief C, et al. Impact of (68)Ga-PSMA PET/CT on the Radiotherapeutic Approach to Prostate Cancer in Comparison to CT: A Retrospective Analysis. *J Nucl Med* (2019) 60(7):963–70. doi: 10.2967/jnumed.118.220855
7. Sonni I, Eiber M, Fendler WP, Alano RM, Vangala SS, Kishan AU, et al. Impact of (68)Ga-PSMA-11 PET/CT on Staging and Management of Prostate Cancer Patients in Various Clinical Settings: A Prospective Single-Center Study. *J Nucl Med* (2020) 61(8):1153–60. doi: 10.2967/jnumed.119.237602
8. Spohn SKB, Kramer M, Kiefer S, Bronsert P, Sigle A, Schultze-Seemann W, et al. Comparison of Manual and Semi-Automatic [(18)F]PSMA-1007 PET Based Contouring Techniques for Intraprostatic Tumor Delineation in Patients With Primary Prostate Cancer and Validation With Histopathology as Standard of Reference. *Front Oncol* (2020) 10:600690. doi: 10.3389/fonc.2020.600690
9. Zamboglou C, Fassbender TF, Steffan L, Schiller F, Fechter T, Carles M, et al. Validation of Different PSMA-PET/CT-Based Contouring Techniques for Intraprostatic Tumor Definition Using Histopathology as Standard of Reference. *Radiother Oncol* (2019) 141:208–13. doi: 10.1016/j.radonc.2019.07.002
10. Hall WA, Paulson E, Davis BJ, Spratt DE, Morgan TM, Dearnaley D, et al. NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes for Intact and Postoperative Prostate Cancer. *Int J Radiat Oncol Biol Phys* (2021) 109(1):174–85. doi: 10.1016/j.ijrobp.2020.08.034
11. Salembier C, Villeirs G, De Bari B, Hoskin P, Pieters BR, Van Vulpen M, et al. ESTRO ACROP Consensus Guideline on CT- and MRI-Based Target Volume Delineation for Primary Radiation Therapy of Localized Prostate Cancer. *Radiother Oncol* (2018) 127(1):49–61. doi: 10.1016/j.radonc.2018.01.014
12. Jethwa KR, Hellekson CD, Evans JD, Harmsen WS, Wilhite TJ, Whitaker TJ, et al. 11c-Choline PET Guided Salvage Radiation Therapy for Isolated Pelvic and Paraortic Nodal Recurrence of Prostate Cancer After Radical Prostatectomy: Rationale and Early Genitourinary or Gastrointestinal Toxicities. *Adv Radiat Oncol* (2019) 4(4):659–67. doi: 10.1016/j.adro.2019.06.006
13. Roach M3rd, Hanks G, Thames HJr., Schellhammer P, Shipley WU, Sokol GH, et al. Defining Biochemical Failure Following Radiotherapy With or Without Hormonal Therapy in Men With Clinically Localized Prostate Cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* (2006) 65(4):965–74. doi: 10.1016/j.ijrobp.2006.04.029

14. Lawton CA, Winter K, Grignon D, Pilepich MV. Androgen Suppression Plus Radiation Versus Radiation Alone for Patients With Stage D1/Pathologic Node-Positive Adenocarcinoma of the Prostate: Updated Results Based on National Prospective Randomized Trial Radiation Therapy Oncology Group 85-31. *J Clin Oncol* (2005) 23(4):800–7. doi: 10.1200/JCO.2005.08.141
15. Mallick I, Das A, Arunsingh M. Moderately Hypofractionated Radiotherapy in Node-Positive Prostate Cancer. *Clin Oncol (R Coll Radiol)* (2019) 31 (4):260–4. doi: 10.1016/j.clon.2019.01.004
16. Emmett L, Tang R, Nandurkar R, Hruby G, Roach P, Watts JA, et al. 3-Year Freedom From Progression After (68)Ga-PSMA PET/CT-Triaged Management in Men With Biochemical Recurrence After Radical Prostatectomy: Results of a Prospective Multicenter Trial. *J Nucl Med* (2020) 61(6):866–72. doi: 10.2967/jnumed.119.235028
17. Briganti A, Karnes JR, Da Pozzo LF, Cozzarini C, Gallina A, Suardi N, et al. Two Positive Nodes Represent a Significant Cut-Off Value for Cancer Specific Survival in Patients With Node Positive Prostate Cancer. A New Proposal Based on a Two-Institution Experience on 703 Consecutive N+ Patients Treated With Radical Prostatectomy, Extended Pelvic Lymph Node Dissection and Adjuvant Therapy. *Eur Urol* (2009) 55(2):261–70. doi: 10.1016/j.eururo.2008.09.043
18. De Bleser E, Tran PT, Ost P. Radiotherapy as Metastasis-Directed Therapy for Oligometastatic Prostate Cancer. *Curr Opin Urol* (2017) 27(6):587–95. doi: 10.1097/MOU.0000000000000441
19. Chu CE, Alshalalfa M, Sjöström M, Zhao SG, Liu Y, Chou J, et al. Prostate-Specific Membrane Antigen and Fluciclovine Transporter Genes Are Associated With Variable Clinical Features and Molecular Subtypes of Primary Prostate Cancer. *Eur Urol* (2021) 79(6):717–21. doi: 10.1016/j.eururo.2021.03.017
20. Hupe MC, Philippi C, Roth D, Kümpers C, Ribbat-Idel J, Becker F, et al. Expression of Prostate-Specific Membrane Antigen (PSMA) on Biopsies Is an Independent Risk Stratifier of Prostate Cancer Patients at Time of Initial Diagnosis. *Front Oncol* (2018) 8:623. doi: 10.3389/fonc.2018.00623
21. Woythal N, Arsenic R, Kempkensteffen C, Miller K, Janssen JC, Huang K, et al. Immunohistochemical Validation of PSMA Expression Measured by (68)Ga-PSMA PET/CT in Primary Prostate Cancer. *J Nucl Med* (2018) 59 (2):238–43. doi: 10.2967/jnumed.117.195172
22. Spohn SKB, Bettermann AS, Bamberg F, Benndorf M, Mix M, Nicolay NH, et al. Radiomics in Prostate Cancer Imaging for a Personalized Treatment Approach - Current Aspects of Methodology and a Systematic Review on Validated Studies. *Theranostics* (2021) 11(16):8027–42. doi: 10.7150/thno.61207
23. Zamboglou C, Carles M, Fechter T, Kiefer S, Reichel K, Fassbender TF, et al. Radiomic Features From PSMA PET for non-Invasive Intraprostatic Tumor Discrimination and Characterization in Patients With Intermediate- and High-Risk Prostate Cancer - A Comparison Study With Histology Reference. *Theranostics* (2019) 9(9):2595–605. doi: 10.7150/thno.32376
24. Kuten J, Fahoum I, Savin Z, Shamni O, Gitstein G, Hershkovitz D, et al. Head-To-Head Comparison of (68)Ga-PSMA-11 With (18)F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. *J Nucl Med* (2020) 61(4):527–32. doi: 10.2967/jnumed.119.234187

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MINI REVIEW
published: 08 June 2022
doi: 10.3389/fonc.2022.932637

Radiotherapy in Oligometastatic, Oligorecurrent and Oligoprogressive Prostate Cancer: A Mini-Review

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Globally, prostate cancer is one of the most common malignancies affecting men. With the advent of advanced molecular imaging, an increasing number of men are found to have oligometastatic disease (OD) either at primary diagnosis or at the time of biochemical failure. No strict definition exists for OD, with historical and ongoing studies utilizing diverse criteria. There is mounting evidence from many different malignancies that patients with OD have improved outcomes compared to their widely metastatic counterparts. As such, treatment intensification of those with OD or oligoprogressive disease has become an area of intense interest and study. This article will review the biology, evidence and controversy behind the treatment of *de novo* oligometastatic, oligorecurrent and oligoprogressive prostate cancer.

Keywords: prostate cancer, radiotherapy, oligometastatic prostate cancer, oligorecurrent prostate cancer, oligoprogressive castration resistant prostate cancer, ADT (androgen deprivation therapy)

OPEN ACCESS

Edited by:
Sophia C. Kamran, Massachusetts General Hospital Cancer Center, United States

Reviewed by:
Nataniel Lester-Coll, University of Vermont, United States

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *30 April 2022*
Accepted: *23 May 2022*
Published: *08 June 2022*

Citation:
Yaney A, Stevens A, Monk P, Martin D, Diaz DA and Wang S-J (2022) Radiotherapy in Oligometastatic, Oligorecurrent and Oligoprogressive Prostate Cancer: A Mini-Review. Front. Oncol. 12:932637. doi: 10.3389/fonc.2022.932637

INTRODUCTION

Prostate cancer is the second most common malignancy and sixth most common cause of cancer-related death among men worldwide (1). Due to the advent of screening prostate-specific antigen (PSA), prostate cancer is typically diagnosed early in the disease course, particularly in developed countries. However, PSA screening recommendations made by the USPSTF in 2012 led to a decline in PSA screening, which resulted in an increase in the incidence of high-risk and metastatic disease at diagnosis, particularly in certain racial and ethnic groups (2–4). While outcomes for low- and intermediate-risk prostate cancer are favorable, a significant proportion of men with high-risk disease will experience recurrence and spread of their cancer (5, 6).

Of those diagnosed with metastatic disease at any point in their disease course, a wide spectrum in total metastatic burden exists, from a single lesion to diffuse disease. Traditionally, systemic therapy has been the mainstay of treatment for these patients, with radiotherapy being used for palliation, if warranted (7, 8). However, recently this treatment paradigm is shifting, particularly in the setting of oligometastatic, oligorecurrent and oligoprogressive disease (9–11).

The aim of this mini-review is to present and summarize the concepts of oligometastatic, oligorecurrent and oligoprogressive prostate cancer in addition to the current evidence on the role of radiotherapy in the management of these distinct disease entities. Evidence to include in this

mini-review was obtained through search of PubMed for peer-reviewed, original studies on prospective trials and clinicaltrials.gov for ongoing/accruing trials in the three distinct oligometastatic disease settings.

BACKGROUND AND DEFINITIONS

While the exact meaning of clinical oligometastatic disease is controversial, most recent clinical trials and clinical reviews have used ≤3-5 metastatic lesions (12). This disease state can be seen either at the time of initial diagnosis (with synchronous metastases), at which point it is considered *de novo* oligometastatic disease, or in the recurrent setting (with metachronous metastases), which is considered oligorecurrent disease (ORD) (12). The exact prevalence of oligometastatic prostate cancer is difficult to describe with any degree of certainty due in part to the lack of a standardized definition, different clinical scenarios in which it can arise (*de novo* or recurrent) and the varying imaging modalities utilized to stage these men (conventional imaging vs. positron emission tomography (PET)-imaging) (10). One study by Larbi et al. utilized whole body MRI to determine the proportion of patients with oligometastatic disease (defined as ≤3 lesions) among 96 men diagnosed with *de novo* metastatic prostate cancer and found that 28% of patients with castration-naïve prostate cancer and 50% of those with castration-resistant disease met criteria for oligometastatic disease (13). Likewise, a study by Müller et al. sought to determine the prevalence of oligometastatic disease (defined as ≤3 lesions) in 110 men with biochemical recurrence after prostatectomy utilizing prostate-specific membrane antigen (PSMA) PET imaging and reported that 30% of patients could be classified as having oligometastatic disease (14).

What is perhaps more important than the clinical definition of oligometastatic disease is its biologic definition and its accompanying implications. Multiple models for the biology of cancer exist, the oldest being the Halsted theory, which proposes that cancer spreads in an orderly fashion from the primary site to regional lymphatics to distant locations (15). In contrast to this, the Fisher theory proposes that cancer is inherently a systemic disease, even if it is evident only locally (16). It is in the third theory of cancer biology, the spectrum theory, in which the concept of oligometastatic disease lies and its importance is highlighted. In this theory, cancer exists in various degrees of clonal evolution, with varying metastatic potential, which evolves over time. In this theory, the concept of oligometastatic disease represents just one timepoint along the evolution of disease, a point which could represent an intermediate state between localized and widely metastatic disease in which cancer cells have limited metastatic potential and thus may be amenable to cure with total elimination of disease burden (12, 17, 18).

The concept of eradication of oligometastatic lesions as a means of improving cancer-specific outcomes has been studied in several malignancies. For instance, surgical resection of liver metastases in addition to primary disease from colorectal cancer confers cure in one of six patients (19). Similarly, local consolidation of primary and oligometastatic sites in both non-small cell lung cancer (NSCLC) and breast cancer have led to significant improvements in or prolongation of progression-free survival (PFS) and overall survival (OS) (19–24). However, management of men with *de novo* or recurrent oligometastatic prostate cancer (OPC) is currently controversial, especially in regard to metastases-directed local therapy. This is reflected by the largely ambiguous guidelines provided in the Prostate Cancer NCCN guidelines, stating that SBRT to metastasis can be considered in the setting of 1) limited metastatic disease when ablation is desired (e.g. impending fracture or encroachment on spinal nerves/vertebrae), 2) in oligometastatic progression when PFS is the primary goal, or 3) if there is a symptomatic lesion in or close to a previously treated region (25). Optimal management of men with *de novo* or recurrent OPC has become more important now than ever due to the advent of advanced molecular imaging, such as PSMA-PET, which has led to an increase in the number of men diagnosed with oligometastatic disease due to its improved sensitivity and specificity over conventional imaging (CI) (26).

On the other hand, oligoprogressive disease is characterized by disease progression in a few sites (again, usually ≤3-5) while on systemic therapy, with the disease biology complicated by selective pressure from systemic treatment. While metastases-directed therapy for both lung and breast cancer in the *de novo* oligometastatic setting appears to be beneficial, recent phase II data suggests that local therapy to oligoprogressive lesions improves outcomes in NSCLC, but not in breast cancer, underscoring the notion that oligometastatic disease is driven by underlying biology rather than a strict clinical definition (27).

The optimal treatment paradigm for oligoprogressive prostate cancer also remains unclear (12). MDT in oligoprogressive prostate cancer is often utilized to delay a change to next-line systemic therapy, although prospective data is lacking to demonstrate outcome benefits of this clinical practice.

RADIOTHERAPY IN *DE NOVO* OLIGOMETASTATIC DISEASE

While available data to guide the use of radiation (RT) in *de novo* OPC is sparse, existing studies sought to address the role of 1) treatment to the primary tumor and 2) treatment to both the primary tumor and oligometastatic sites (see **Table 1**). STAMPEDE Arm H examined the use of radiotherapy to the primary tumor in men with newly diagnosed metastatic prostate cancer. In this study, 2,061 men with metastatic prostate cancer (mPCa) of any metastatic disease burden were randomized to systemic therapy (androgen deprivation therapy (ADT) alone from 01/2013 to 12/2015, with docetaxel allowed in addition to ADT from 12/2015 onward) with or without RT to the prostate to either 36 Gy in 6 fractions given once weekly or 55 Gy in 20 fractions delivered over 4 weeks. While the primary endpoint of OS difference was not significant between the RT and no RT arms, subgroup analysis showed a significant improvement in OS

TABLE 1 | Prospective trials evaluating the role of radiotherapy in (oligo)metastatic prostate cancer.

Study	Disease Type	Metastatic Burden	Study Type	N	Randomization (if applicable)	Primary Outcome	Result	Toxicity
STAMPEDE Arm H	*De novo* metastatic disease	Any metastatic burden	Phase III RCT	2,061	ADT (+/- docetaxel) vs. ADT (+/- docetaxel) with prostate RT	OS	OS difference not significant overall (HR 0.92, 95% CI 0.80-1.06). Subgroup analysis showed significant benefit in OS for those with low metastatic burden (HR 0.68, 95% CI 0.52-0.9; p=0.007)*	G3 or G4 in 5% of patients
HORRAD	*De novo* metastatic disease	Any metastatic burden	Phase III RCT	432	ADT alone vs. ADT with prostate RT	OS	OS difference not significant (HR=0.90, 95% CI 0.70-1.14)	Not reported
SABR-COMET	ORD	1-5 metastases	Phase II RCT	99**	MDT vs. Standard of care for their respective malignancies	OS	OS improved in MDT arm (5-year OS 42.3% vs. 17.7%, p=0.006)	G5 in 4.5% of patients
STOMP	ORD	≤ 3 metastases	Phase II RCT	62	MDT vs. Observation	ADT-free survival	Median ADT-free survival improved in MDT arm (5-year ADT-free survival 34% vs. 8%, p=0.06)	No G2 or higher
ORIOLE	ORD	≤ 3 metastases	Phase II RCT	54	MDT vs. Observation	Rate of disease progression at 6 months	Disease progression was improved in MDT cohort (Progression at 6 months 19% vs. 61%, p=0.005)	No G3 or higher toxicities
Glicksman et al.	ORD	No limit	Single-arm Phase II Trial	37	PSMA-PET-guided MDT with SBRT or surgery, without ADT	Biochemical response	60% overall response rate with 22% having complete response	No G3 or higher toxicities
Kneebone et al.	ORD	1-3 nodal or bone metastases	Single-arm Phase II Clinical Trial	57	SBRT to metastatic sites without ADT	Biochemical failure***	At median follow up of 16 months, median bDFS was 11 months, with 31.9% bDFS at 15 months	No G3 or higher
Siva et al.	ORD	1-3 nodal or bone metastases	Feasibility Study	33	One fraction of SBRT to each lesion	Feasibility and tolerability	All but one patient completed the prescribed dose to metastatic sites	One patient with G3
Pezzulla et al.	OPD	≤ 5 non-visceral, nodal metastases	*Post hoc* analysis of phase I clinical trials	38	SBRT to lesions (in addition to concurrent ADT)	Biochemical response and toxicity	2-year next line systemic therapy-free survival of 67.7%	One patient with > G1

**Defined as not having visceral metastases or ≥4 bone metastases with at least one outside of the spine/pelvis.*

***N=16 with prostate cancer.*

****PSA level of nadir +0.2ng/mL following MDT.*

RCT, randomized controlled trial; ADT, androgen deprivation therapy; OS, overall survival; OMD, oligometastatic disease; RT, radiotherapy; ORD, oligorecurrent disease; MDT, metastasis-directed therapy; SBRT, stereotactic body radiotherapy; OPD, oligoprogressive disease; G#, grade #.

in men who received prostate RT in the setting of low-volume metastatic disease as per the CHAARTED trial (defined as not having visceral metastases or ≥4 bone metastases with at least one outside of the spine/pelvis; HR 0.68, 95% CI 0.52-0.9; p=0.007), indicating a potential benefit of primary site local therapy in the setting of *de novo* OPC. Subsequently, an exploratory analysis of STAMPEDE Arm H using a more refined definition of metastatic disease burden was performed. In this analysis, patients with non-regional lymph node or ≤3 bone metastases were found to have improved OS (HR 0.62, 95% CI 0.46-0.83 vs. 1.08, 95% CI 0.91-1.28, p=0.003, respectively) and failure-free survival (0.57, 95% CI 0.47-0.70 vs. 0.87, 95% CI 0.76-0.99, p=0.002, respectively) compared to those with ≥4 bone or any visceral metastases (9). Furthermore, of 1939 men with skeletal metastases, the benefit of local therapy continuously decreased with increasing number of lesions (28). Importantly, only 5% of patients in the radiotherapy arm reported a grade 3 (G3) or grade 4 (G4) toxicity and no grade 5 (G5) toxicities were noted, indicating that the potential benefit of local therapy in OPC is not offset by significant toxicity (9, 29). Along with showing clinical benefit, local therapy appears to be cost-effective. Lester-Coll et al. conducted a cost-effectiveness study utilizing data from men with low-burden metastatic disease utilizing STAMPEDE Arm H data and found that the inclusion of prostate-directed radiotherapy in addition to ADT was associated with higher quality-adjusted life years at a lower cost than ADT alone, with a savings of >$30,000 with lifetime follow-up (30).

HORRAD is another phase III study that examined the effect of local treatment to the prostate in the setting of *de novo* OPC. 432 men with previously untreated *de novo* mPCa, PSA>20 ng/mL and unlimited bone metastases were randomized to either ADT alone or ADT with RT to the primary tumor consisting of either 70 Gy in 35 fractions given over 7 weeks or 57.76 Gy in 19

fractions given three times per week. The primary endpoint, OS, was not significant between the two arms (HR=0.90, 95% CI 0.70-1.14). Moreover, subgroup analysis of patients with fewer than 5 metastases also did not demonstrate a statistically significant difference in OS (HR 0.68, 95% CI 0.42-1.10) (31). While this may cast doubt on the benefit of local therapy in the oligometastatic setting, it is imperative to note that a pooled analysis of the STAMPEDE and HORRAD trials showed a 7% improvement in 3-year survival in men with fewer than 5 bone metastases (32). The role of local therapy in the setting of metastatic disease is further being explored in the prospective trials PEACE-1 and SWOG 1802, although the eligibility for either trial include patients with any number of metastatic lesions, making their relevance in OPC uncertain at this time (33, 34).

The concept of treating both the primary tumor in addition to metastasis-directed therapy (MDT), or total consolidative therapy (TCT), is gaining traction in OPC. Most data regarding TCT comes from small, retrospective studies. For instance, one experience from the University of Rome consisting of 37 previously radiotherapy-naïve patients with ≤5 metastases who underwent TCT showed promising results, with OS and biochemical relapse-free survival (b-RFS) at 5 years of 65.4% and 39.3%, respectively, with no instances of ≥G3 acute or late toxicity reported (35). A separate retrospective study reported by Deantoni et al. included 39 men with bone-only (≤2) metastases showed similarly favorable outcomes with TCT, with 4-year rates of b-RFS and OS of 53.3% and 82.4%, respectively. In this study, no acute ≥G3 toxicities were noted, and no toxicity of any severity was reported for treatment of metastatic sites (36). The only prospective evidence for TCT in OPC comes from a single prospective registry trial that consisted of 12 men with *de novo* OPC (≤5 metastases) who underwent sequential treatment with neoadjuvant chemotherapy, radical prostatectomy, MDT+/- adjuvant RT to the prostatic bed/pelvis followed by adjuvant ADT. At 3 years, 67% of men were free from biochemical failure and all remained alive, with no ≥G3 acute toxicities and no late toxicity of any severity reported (37). An ongoing small single-arm phase II trial (NCT03298087) is also evaluating the efficacy of TCT in *de novo* OPC patients with prostatectomy, MDT to metastatic lesions, and adjuvant radiotherapy with 6-months of ADT, apalutamide and abiraterone, with final results not yet reported (**Table 2**) (38). Taken together, these studies suggest that TCT for men with *de*

TABLE 2 | Ongoing/future trials evaluating radiotherapy/MDT in (oligo)metastatic prostate cancer.

Study	Disease Type	Metastatic Burden	Study Type	Randomization (if applicable)	Primary Outcome
STAMPEDE Arm M	*De novo* OMD	≤5 lesions	Phase III RCT	SOC (+ prostate RT/surgery) vs. SOC (+ prostate RT/surgery) + MDT	OS
NCT03298087	*De novo* OMD	≤5 lesions	Single-arm Phase II	Prostatectomy + MDT + adjuvant RT with 6 months of ADT/apalutamide/abiraterone	PSA <0.05ng/mL 6 months after recovery of testosterone
PLATON	*De novo* OMD and ORD	≤5 lesions	Phase III RCT	SOC* vs. SOC* + MDT	FFS at 6 years
NRG-GU011	ORD	≤5 lesions	Phase II RCT	MDT + placebo vs. MDT + relugolix	rPFS by conventional imaging
DART	ORD	≤5 lesions	Phase II RCT	MDT vs. MDT + darolutamide	MFS at 2 years by PET
RADIOSA	ORD	≤3 lesions	Phase II RCT	MDT vs. MDT + LHRH agonist/antagonist	PFS
ECOG-ACRIN 8191	Biochemical recurrence	No limit**	Phase III RCT	Salvage RT + ADT/apalutamide vs. Salvage RT + ADT/apalutamide + MDT	PFS, QOL
FORCE	OPD	≤5 lesions	Phase II RCT	SOC vs. SOC + SBRT to all sites of disease	Mean response duration
PEACE-1	*De novo* metastatic disease	No limit	Phase III RCT	SOC (ADT +/- docetaxol) vs. SOC + abiraterone vs. SOC + prostate RT vs. SOC + abiraterone + prostate RT	OS, rPFS

**SOC includes ablative therapy (surgery or SBRT) to prostate for patients with untreated prostate primary and low volume metastatic disease. **Conventional imaging negative, no limit on 18F-fluciclovine PET positive lesions.*

OMD, oligometastatic disease; RCT, randomized controlled trial; SOC, standard of care; MDT, metastasis-directed therapy; OS, overall survival; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; ORD, oligorecurrent disease; SBRT, stereotactic body radiotherapy; FFS, failure-free survival; rPFS, radiographic progression-free survival; MFS, metastasis-free survival; LHRH, luteinizing hormone-releasing hormone; PFS, progression-free survival; QOL, quality of life; OPD, oligoprogressive disease; RT, radiotherapy.

novo OPC may be a feasible management strategy with low risk of clinically significant toxicity.

While the previously discussed studies offer promise regarding the potential for TCT in the setting of OPC, phase III trials remain the gold standard to evaluate the benefit of MDT in addition to local therapy to the prostate for men with OPC. One such future trial is STAMPEDE Arm M that will enroll men with *de novo* OPC who plan to undergo local therapy (surgery or RT) and will be randomized to receiving systemic therapy with or without MDT, with those receiving MDT effectively receiving TCT (**Table 2**). However, it is imperative to note that *de novo* OPC in STAMPEDE Arm M is being defined by CI only, rather than by more sensitive molecular imaging such as PSMA-PET, leaving the question of how to optimally manage men with *de novo* OPC defined by PSMA-PET unanswered (39). The ongoing phase III Canadian PLATON trial (NCT03784755) also defines *de novo* or recurrent OPC using CI and randomizes these patients to with or without MDT (40). Designing future trials to assess the efficacy of PET-guided MDT in *de novo* OPC is warranted to complement the results from these CI-defined OPC trials, especially with the recent rapid adoption of PSMA-PET for upfront initial staging.

RADIOTHERAPY IN OLIGORECURRENT DISEASE (ORD)

Most evidence for MDT in oligometastatic disease comes from phase II RCTs in the setting of ORD, although the diversity of primary endpoints among studies can make the clinical application of RT unclear (see **Table 1**). One such trial is the SABR-COMET, in which 99 patients with ORD from various malignancies with 1-5 metastases underwent a 2:1 randomization to MDT with stereotactic radiotherapy vs. SOC for their respective malignancies, with a primary endpoint of OS. It is important to note that only 16 of the 99 patients included in this trial had prostate cancer. At 5 years, OS was 42.3% in the MDT arm compared to only 17.7% who were treated with SOC. While this appears to be an impressive improvement in OS with the addition of MDT, this study is not without criticisms. First, given that this study included multiple histologies, with prostate cancer representing only a small fraction, it is difficult to apply these results to all patients with oligorecurrent prostate cancer. Moreover, there was a skewed proportion of prostate cancer patients between the two arms, with prostate cancer patients comprising 21% of those who received MDT compared to only 6% of those who received SOC. The favorable natural history of prostate cancer may have led to a higher OS rate in the MDT arm. A final criticism of this study is that the rate of G5 toxicity was 4.5% in those treated with MDT, which is exceedingly high and not consistent with the plethora of evidence that supports the safety of MDT, although none of these deaths occurred in patients with prostate cancer. Of note, 2/3 of G5 toxicities occurred in patients undergoing thoracic SBRT, which is uncommon in the setting of mPCa (41, 42).

Many of the concerns regarding SABR-COMET and its relevance to men with prostate ORD can be addressed by having a more homogeneous study population. STOMP is a phase II RCT that randomized 62 men with prostate cancer who had asymptomatic ORD, defined as 3 or fewer metastases on choline-PET, after prior primary curative therapy in a 1:1 fashion to MDT or observation. The primary outcome of this study was ADT-free survival, with indications to start ADT for symptomatic or local progression or development of additional metastases. At a median follow up of 3 years, median ADT-free survival was 13 months in the surveillance cohort compared to 21 months for those who received MDT (HR 0.60, 80% CI 0.40-0.90, p=0.11). Of note, in contrast to the severe toxicities noted in SABR-COMET, no G2-5 toxicities were reported in this study (43). ORIOLE is another phase II RCT that utilized MDT in the oligorecurrent setting. This trial randomized 54 men with hormone-sensitive mPCa with ≤3 metastases based on CI in a 2:1 fashion to MDT with SBRT or observation. The study's primary outcome was the rate of disease progression at 6 months, which was significantly improved in the MDT cohort compared to the observation group (19% vs. 61%, p=0.005). Again, in contrast to SABR-COMET, no G3 or greater toxicities were reported in this study (44).

Several smaller single-arm prospective studies have also demonstrated the safety and efficacy of MDT in ORD. A study by Glicksman et al. enrolled patients with rising PSA after radical prostatectomy and either adjuvant or salvage RT who had negative CI but positive PSMA-PET findings on restaging scans. Patients were treated with PSMA-PET-guided MDT with SBRT (n=27) or surgery (n=10) without ADT. At a median follow up of 15.9 months, 22% of treated men had an undetectable PSA, with a 60% overall response rate and a median time to PSA progression of 17.7 months, allowing for further delay in ADT administration. No G3 or greater toxicities were noted in patients who received SBRT (45). Similarly, a study by Kneebone et al. treated 57 oligorecurrent patients with 1-3 metastatic nodal or bone sites detected *via* PSMA-PET with SBRT to the metastatic sites without ADT. The primary endpoint was biochemical failure, defined as PSA level of nadir +0.2ng/mL following MDT. At a median follow-up of 16 months, the median biochemical disease-free survival (bDFS) was 11 months, with 31.9% bDFS at 15 months. No G3 or higher toxicities were noted in this study (46). A separate feasibility study by Siva et al. treating 33 patients with 1-3 metastases by NaF-PET and CI also showed favorable results with or without ADT, with all but one patient completing the prescribed 20 Gy in 1 fraction dose to sites of metastatic disease. Two-year distant PFS was 39%, and 48% of those treated without ADT remained free from ADT at 2 years. Only one G3 toxicity was reported (47).

The use of MDT in ORD is not only clinically beneficial but can also be a cost-effective treatment strategy. One cost-utility analysis based on the STOMP trial showed that MDT appeared to have an 85.9% probability of being cost-effective in comparison to surveillance with delayed ADT and a 100% probability of cost-effectiveness in comparison to immediate

ADT (48). A separate study utilizing the SABR-COMET clinical data found that MDT was cost-effective in 97% of all iterations in comparison to standard of care on probabilistic sensitivity analysis. While SABR-COMET was based in Canada, an additional analysis was performed based on United States payer perspective and yielded similar results with a 98% probability of cost-effectiveness (49).

Taken as a whole, these studies evaluating the use of MDT in the setting of oligorecurrent prostate cancer demonstrate that MDT is a cost-effective treatment strategy associated with minimal toxicity and the potential to delay disease progression and the use of ADT/systemic therapy. Furthermore, for a subset of patients, albeit likely small, MDT for ORD may even achieve long-term disease control. However, prospective phase III studies are warranted to further investigate the clinical benefit of MDT in this setting. Currently, several phase II trials are ongoing to evaluate the potential benefit of combining a short-course of hormonal therapy with MDT to improve disease control (**Table 2**). NRG-GU011 (NCT05053152), DART (NCT04641078), and RADIOSA (NCT03940235) aim to investigate the addition of relugolix, darolutamide, and LHRH agonists/antagonists, respectively, to MDT (50–52). On the other hand, in the setting of biochemical recurrence after prostatectomy, phase III ECOG-ACRIN 8191 seeks to evaluate the role of MDT in patients with CI-negative but 18F-fluciclovine PET-positive extra-pelvic metastases at time of PSA progression, which addresses a timely question of whether local therapy of PET-detected metastatic disease (of lower tumor burden compared to CI-detected disease) will alter patient outcomes (**Table 2**) (53).

RADIOTHERAPY IN (OPD) OLIGOPROGRESSIVE DISEASE

With the advent of systemic therapy options that have led to prolonged survival compared to historical standards, even in men with widespread metastatic disease, there has been growing interest in the use of radiotherapy for OPD, with the rationale being that treating sites of oligoprogression may allow patients to remain on the same agent for a longer duration by eradicating tumor clones that have developed resistance to the agent (11). However, no large prospective study exists on the clinical utility of radiotherapy in the setting of OPD, although a prospective trial is currently accruing (**Table 2**). The main source of prospective data regarding OPD is a pooled analysis of two phase I studies that assessed the use of stereotactic RT in primary, oligorecurrent and oligometastatic cancers. This analysis included men with metastatic castration-resistant prostate cancer (mCR-PCa) with 5 or fewer metastases (without visceral metastases) and progressive nodal metastases. In total, 38 patients were included, all of whom were receiving ADT at time of treatment. Two-year next line systemic therapy-free survival (NEST-FS) was 67.7% and only one patient had a >G1 toxicity (G2 dysphagia for supraclavicular field treatment) (54). Beyond this, one must look to retrospective studies for further data. Herein, a subset of these studies will be discussed. One retrospective study by Onal et al. reviewed 54 men with mCR-PCa with 5 or fewer PSMA-PET or bone scan-detected progressive lesions in the lymph nodes or bones treated with SBRT to all lesions while receiving abiraterone or enzalutamide. With a median follow-up of 19.1 months, median prostate cancer-specific survival (PCSS) and PFS were 27.8 months and 12.7 months, respectively. Of note, the number of oligoprogressive lesions requiring treatment and the time between start of abiraterone or enzalutamide and RT treatment were prognostic factors for PCSS on univariate analysis, although the number of lesions treated was only borderline significant on multivariate analysis (p=0.06). Further supporting the use of RT to delay a change in systemic therapy, SBRT to oligoprogressive lesions allowed for continuation of the patients' current systemic therapies for a median of 8.6 months (11). A second retrospective study by Onal et al. of 67 patients treated with SBRT to 5 or fewer PSMA-positive oligoprogressive lesions showed similarly favorable results, with 2-year OS of 86.9% and only 32.8% of patients progressing to next-line systemic therapy at a median time of 16.4 months from completing SBRT (55).

Likewise, Deek et al. reported outcomes of 68 patients with mCR-PCa who received RT to 1-5 progressive lesions. Following MDT, median time to PSA recurrence, time to next intervention and distant metastasis-free survival were 9.67 months, 15.6 months and 10.8 months, respectively. Median OS had not been reached at median follow-up of 30.9 months. Of note, patients with consolidation of all disease (progressive and stable lesions) were also included in this study, with those receiving TCT having improved outcomes compared to those treated to oligoprogressive lesions alone (56). Additional retrospective studies have shown similar findings with MDT to oligoprogressive sites delaying the need to change systemic therapy, with reported median time to NEST-FS of 15.2 months (57), 16 months (58) and 21.8 months (59), and prolonged distant progression-free survival of 21.6% at 2-years (60).

While additional prospective evidence is needed to further clarify the role of RT in oligoprogressive prostate cancer, these retrospective studies demonstrating a prolongation of NEST-FS and/or PFS suggest that MDT to oligoprogressive sites of disease is a potential treatment strategy that may increase the effective time-window of any given systemic therapy for at least a subset of men with OPD. The phase II FORCE trial seeks to further explore this notion in a different light. Rather than examining NEST-FS or PFS without changing systemic therapy, the primary objective of FORCE trial is to assess the mean duration of response of men with oligometastatic castrate-resistant disease receiving next-line systemic therapy randomized to with or without MDT (61). Certainly, more prospective trials are necessary in the OPD setting to optimize the use of MDT to maximize the utility of systemic therapies available for castrate-resistant disease.

CONCLUSION

While the role of RT in *de novo* OPC, ORD and OPD remains unclear, clinically meaningful outcomes have been

demonstrated with MDT to OPD and ORD. Larger trials are needed to answer several questions, including which patients will not benefit from this strategy and which patients stand to receive the most benefit, perhaps even cure. With various ongoing studies in this realm currently underway (**Table 2**), the clinical benefit of MDT in the oligometastatic setting will likely be further clarified soon.

AUTHOR CONTRIBUTIONS

AY and S-JW contributed to the conception and outline of the manuscript design. AY and S-JW wrote the manuscript. AS, AY, and S-JW generated the tables. All authors contributed to manuscript revision, read, and approved the submitted version.

REFERENCES

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. *Eur Urol* (2020) 77 (1):38–52. doi: 10.1016/j.eururo.2019.08.005
2. Taitt HE. Global Trends and Prostate Cancer: A Review of Incidence, Detection, and Mortality as Influenced by Race, Ethnicity, and Geographic Location. *Am J Mens Health* (2018) 12(6):1807–23. doi: 10.1177/1557988318798279
3. Fletcher SA, von Landenberg N, Cole AP, Gild P, Choueiri TK, Lipsitz SR, et al. Contemporary National Trends in Prostate Cancer Risk Profile at Diagnosis. *Prostate Cancer Prostatic Dis* (2020) 23(1):81–7. doi: 10.1038/s41391-019-0157-y
4. Kensler KH, Pernar CH, Mahal BA, Nguyen PL, Trinh QD, Kibel AS, et al. Racial and Ethnic Variation in PSA Testing and Prostate Cancer Incidence Following the 2012 USPSTF Recommendation. *J Natl Cancer Inst* (2021) 113 (6):719–26. doi: 10.1093/jnci/djaa171
5. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes After Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med* (2016) 375(15):1415–24. doi: 10.1056/NEJMoa1606220
6. Moris L, Cumberbatch MG, Van den Broeck T, Gandaglia G, Fossati N, Kelly B, et al. Benefits and Risks of Primary Treatments for High-Risk Localized and Locally Advanced Prostate Cancer: An International Multidisciplinary Systematic Review. *Eur Urol* (2020) 77(5):614–27. doi: 10.1016/j.eururo.2020.01.033
7. Teo MY, Rathkopf DE, Kantoff P. Treatment of Advanced Prostate Cancer. *Annu Rev Med* (2019) 70:479–99. doi: 10.1146/annurev-med-051517-011947
8. Catton CN, Gospodarowicz MK. Palliative Radiotherapy in Prostate Cancer. *Semin Urol Oncol* (1997) 15(1):65–72.
9. *Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer (STAMPEDE): A Randomised Controlled Phase 3 Trial - ScienceDirect* . Available at: https://www.sciencedirect.com/science/article/pii/S0140673618324863?via%3Dihub (Accessed 2022 Mar 4).
10. Rao A, Vapiwala N, Schaeffer EM, Ryan CJ. Oligometastatic Prostate Cancer: A Shrinking Subset or an Opportunity for Cure? *Am Soc Clin Oncol Educ Book* (2019) 39):309–20. doi: 10.1200/EDBK_239041
11. Onal C, Kose F, Ozyigit G, Aksoy S, Oymak E, Muallaoglu S, et al. Stereotactic Body Radiotherapy for Oligoprogressive Lesions in Metastatic Castration-Resistant Prostate Cancer Patients During Abiraterone/Enzalutamide Treatment. *Prostate.* (2021) 81(9):543–52. doi: 10.1002/pros.24132
12. Foster CC, Weichselbaum RR, Pitroda SP. Oligometastatic Prostate Cancer: Reality or Figment of Imagination? *Cancer* (2019) 125(3):340–52. doi: 10.1002/cncr.31860
13. Larbi A, Dallaudière B, Pasoglou V, Padhani A, Michoux N, Vande Berg BC, et al. (WB-MRI) Assessment of Metastatic Spread in Prostate Cancer: Therapeutic Perspectives on Targeted Management of Oligometastatic Disease. *Prostate.* (2016) 76(11):1024–33. doi: 10.1002/pros.23196
14. Müller PJ, Dietlein M, Kobe C, Heidenreich A, Drzezga A. Oligometastatic Disease in Biochemical Recurrence of Prostate Cancer: Prevalence on PSMA PET/CT and Consecutive Metastasis-Directed Therapy - Experience at a Tertiary Referral Center. *Nukl Nucl Med* (2022). doi: 10.1055/a-1697-8111
15. Halsted WSI. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital From June, 1889, to January, 1894. *Ann Surg* (1894) 20(5):497–555. doi: 10.1097/00000658-189407000-00075
16. Fisher B. Laboratory and Clinical Research in Breast Cancer–a Personal Adventure: The David A. Karnofsky Memorial Lecture. *Cancer Res* (1980) 40(11):3863–74.
17. Hellman S. Karnofsky Memorial Lecture. Natural History of Small Breast Cancers. . *J Clin Oncol Off J Am Soc Clin Oncol* (1994) 12(10):2229–34. doi: 10.1200/JCO.1994.12.10.2229
18. Deek MP, van der Eecken K, Phillips R, Parikh NR, Isaacsson Velho P, Lotan TL, et al. The Mutational Landscape of Metastatic Castration-Sensitive Prostate Cancer: The Spectrum Theory Revisited. *Eur Urol* (2021) 80 (5):632–40. doi: 10.1016/j.eururo.2020.12.040
19. Tomlinson JS, Jarnagin WR, DeMatteo RP, Fong Y, Kornprat P, Gonen M, et al. Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure. *J Clin Oncol* (2007) 25(29):4575–80. doi: 10.1200/JCO.2007.11.0833
20. Gomez DR, Tang C, Zhang J, Blumenschein GR, Hernandez M, Lee JJ, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol* (2019) 37(18):1558–65. doi: 10.1200/JCO.19.00201
21. Wang XS, Bai YF, Verma V, Yu RL, Tian W, Ao R, et al. Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic EGFR-Mutated NSCLC. *J Natl Cancer Inst* (2022) djac015. doi: 10.1093/jnci/djac015
22. Trovo M, Furlan C, Polesel J, Fiorica F, Arcangeli S, Giaj-Levra N, et al. Radical Radiation Therapy for Oligometastatic Breast Cancer: Results of a Prospective Phase II Trial. *Radiother Oncol J Eur Soc Ther Radiol Oncol* (2018) 126(1):177–80. doi: 10.1016/j.radonc.2017.08.032
23. Milano MT, Katz AW, Zhang H, Huggins CF, Aujla KS, Okunieff P. Oligometastatic Breast Cancer Treated With Hypofractionated Stereotactic Radiotherapy: Some Patients Survive Longer Than a Decade. *Radiother Oncol J Eur Soc Ther Radiol Oncol* (2019) 131:45–51. doi: 10.1016/j.radonc.2018.11.022
24. Franzese C, Comito T, Viganò L, Pedicini V, Franceschini D, Clerici E, et al. Liver Metastases-Directed Therapy in the Management of Oligometastatic Breast Cancer. *Clin Breast Cancer.* (2020) 20(6):480–6. doi: 10.1016/j.clbc.2020.05.006
25. National Comprehensive Cancer Network. *Prostate Cancer* . Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
26. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-Specific Membrane Antigen PET-CT in Patients With High-Risk Prostate Cancer Before Curative-Intent Surgery or Radiotherapy (proPSMA): A Prospective, Randomised, Multicentre Study. *Lancet Lond Engl* (2020) 395 (10231):1208–16. doi: 10.1016/S0140-6736(20)30314-7
27. Tsai CJ, Yang JT, Guttmann DM, Shaverdian N, Shepherd AF, Eng J, et al. Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression —— Interim Analysis of the First Randomized Study of Stereotactic Body Radiotherapy in Patients With Oligoprogressive Metastatic Cancers of the Lung and Breast. *Int J Radiat Oncol* (2021) 111(5):1325–6. doi: 10.1016/j.ijrobp.2021.09.014
28. Ali A, Hoyle A, Haran ÁM, Brawley CD, Cook A, Amos C, et al. Association of Bone Metastatic Burden With Survival Benefit From Prostate Radiotherapy in Patients With Newly Diagnosed Metastatic Prostate Cancer: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Oncol* (2021) 7(4):555–63. doi: 10.1001/jamaoncol.2020.7857
29. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805

CHAARTED Trial. *J Clin Oncol Off J Am Soc Clin Oncol* (2018) 36(11):1080–7. doi: 10.1200/JCO.2017.75.3657
30. Lester-Coll NH, Ades S, Yu JB, Atherly A, Wallace HJ, Sprague BL. Cost-Effectiveness of Prostate Radiation Therapy for Men With Newly Diagnosed Low-Burden Metastatic Prostate Cancer. *JAMA Netw Open* (2021) 4(1): e2033787. doi: 10.1001/jamanetworkopen.2020.33787
31. Boevé LMS, Hulshof MCCM, Vis AN, Zwinderman AH, Twisk JWR, Witjes WPJ, et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined With Concurrent Radiation Therapy to the Prostate in Patients With Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data From the HORRAD Trial. *Eur Urol* (2019) 75(3):410–8. doi: 10.1016/j.eururo.2018.09.008
32. Burdett S, Boevé LM, Ingleby FC, Fisher DJ, Rydzewska LH, Vale CL, et al. Prostate Radiotherapy for Metastatic Hormone-Sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-Analysis. *Eur Urol* (2019) 76(1):115–24. doi: 10.1016/j.eururo.2019.02.003
33. *S1802 SWOG* . Available at: https://www.swog.org/clinical-trials/s1802 (Accessed 2022 Mar 29).
34. UNICANCER. *A Prospective Randomised Phase III Study Of Androgen Deprivation Therapy With Or Without Docetaxel With Or Without Local Radiotherapy With Or Without Abiraterone Acetate And Prednisone In Patients With Metastatic Hormone-Naïve Prostate Cancer* (2021). Available at: https://clinicaltrials.gov/ct2/show/NCT01957436 (Accessed 2022 Mar 28).
35. Reverberi C, Massaro M, Osti MF, Anzellini D, Marinelli L, Montalto A, et al. Local and Metastatic Curative Radiotherapy in Patients With *De Novo* Oligometastatic Prostate Cancer. *Sci Rep* (2020) 10(1):17471. doi: 10.1038/s41598-020-74562-3
36. Deantoni CL, Fodor A, Cozzarini C, Fiorino C, Brombin C, Di Serio C, et al. Prostate Cancer With Low Burden Skeletal Disease at Diagnosis: Outcome of Concomitant Radiotherapy on Primary Tumor and Metastases. *Br J Radiol* (2020) 93(1108):20190353. doi: 10.1259/bjr.20190353
37. Reyes DK, Rowe SP, Schaeffer EM, Allaf ME, Ross AE, Pavlovich CP, et al. Multidisciplinary Total Eradication Therapy (TET) in Men With Newly Diagnosed Oligometastatic Prostate Cancer. *Med Oncol Northwood Lond Engl* (2020) 37(7):60. doi: 10.1007/s12032-020-01385-7
38. VA Office of Research and Development. *Systemic and Tumor-Directed Therapy for Oligometastatic Prostate Cancer* (2022). Available at: https://clinicaltrials.gov/ct2/show/NCT03298087 (Accessed 2022 Apr 18).
39. Preisser F, Chun F, Banek S, Wenzel M, Graefen M, Steuber T, et al. Management and Treatment Options for Patients With *De Novo* and Recurrent Hormone-Sensitive Oligometastatic Prostate Cancer. *Prostate Int* (2021) 9(3):113–8. doi: 10.1016/j.prnil.2020.12.003
40. Canadian Cancer Trials Group. *A Randomized Phase III Trial of Local Ablative Therapy For Hormone Sensitive Oligometastatic Prostate Cancer [PLATON]* (2022). Available at: https://clinicaltrials.gov/ct2/show/NCT03784755 (Accessed 2022 Apr 18).
41. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J Clin Oncol Off J Am Soc Clin Oncol* (2020) 38(25):2830–8. doi: 10.1200/JCO.20.00818
42. Sogono P, Ball DL, Siva S. SABR-COMET: A New Paradigm of Care Lights Up the Twilight of Metastatic Disease. *Ann Transl Med* (2019) 7(22):615–5. doi: 10.21037/atm.2019.10.96
43. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol* (2018) 36(5):446–53. doi: 10.1200/JCO.2017.75.4853
44. Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol* (2020) 6(5):650–9. doi: 10.1001/jamaoncol.2020.0147
45. Glicksman RM, Metser U, Vines D, Valliant J, Liu Z, Chung PW, et al. Curative-Intent Metastasis-Directed Therapies for Molecularly-Defined Oligorecurrent Prostate Cancer: A Prospective Phase II Trial Testing the Oligometastasis Hypothesis. *Eur Urol* (2021) 80(3):374–82. doi: 10.1016/j.eururo.2021.02.031
46. Kneebone A, Hruby G, Ainsworth H, Byrne K, Brown C, Guo L, et al. Stereotactic Body Radiotherapy for Oligometastatic Prostate Cancer Detected *via* Prostate-Specific Membrane Antigen Positron Emission Tomography. *Eur Urol Oncol* (2018) 1(6):531–7. doi: 10.1016/j.euo.2018.04.017
47. Siva S, Bressel M, Murphy DG, Shaw M, Chander S, Violet J, et al. Stereotactic Abative Body Radiotherapy (SABR) for Oligometastatic Prostate Cancer: A Prospective Clinical Trial. *Eur Urol* (2018) 74(4):455–62. doi: 10.1016/j.eururo.2018.06.004
48. De Bleser E, Willems R, Decaestecker K, Annemans L, De Bruycker A, Fonteyne V, et al. A Trial-Based Cost-Utility Analysis of Metastasis-Directed Therapy for Oligorecurrent Prostate Cancer. *Cancers* (2020) 12(1): E132. doi: 10.3390/cancers12010132
49. Qu XM, Chen Y, Zaric GS, Senan S, Olson RA, Harrow S, et al. Is SABR Cost-Effective in Oligometastatic Cancer? An Economic Analysis of the SABR-COMET Randomized Trial. *Int J Radiat Oncol Biol Phys* (2021) 109(5):1176–84. doi: 10.1016/j.ijrobp.2020.12.001
50. Phase AII Double-Blinded. *Placebo Controlled Trial of Prostate Oligometastatic Radiotherapy With or Without Androgen Deprivation Therapy in Oligometastatic Prostate Cancer (NRG Promethean)* . Available at: https://www.nrgoncology.org/Clinical-Trials/Protocol/nrg-gu011?filter=nrg-gu011 (Accessed 2022 Apr 13).
51. University Hospital. *Ghent. Stereotactic Body Radiotherapy With or Without Darolutamide for OligoRecurrent Prostate Cancer: A Randomized Phase II Trial (DART)* (2021). Available at: https://clinicaltrials.gov/ct2/show/NCT04641078 (Accessed 2022 Apr 18).
52. European Institute of Oncology. *Radioablation +/- Hormonotherapy for Prostate Cancer Oligorecurrences (RADIOSA Trial): Potential of Imaging and Biology* (2021). Available at: https://clinicaltrials.gov/ct2/show/NCT03940235 (Accessed 2022 Apr 18).
53. Cancer Research Group ECOG-ACRIN. *Phase III Study of Local or Systemic Therapy INtensification DIrected by PET in Prostate CAncer Patients With Post-ProstaTEctomy Biochemical Recurrence (INDICATE)* . Available at: https://clinicaltrials.gov/ct2/show/NCT04423211 (Accessed 2022 Apr 12).
54. Pezzulla D, Macchia G, Cilla S, Buwenge M, Ferro M, Bonome P, et al. Stereotactic Body Radiotherapy to Lymph Nodes in Oligoprogressive Castration-Resistant Prostate Cancer Patients: A *Post Hoc* Analysis From Two Phase I Clinical Trials. *Clin Exp Metastasis* (2021) 38(6):519–26. doi: 10.1007/s10585-021-10126-7
55. Onal C, Ozyigit G, Oymak E, Guler OC, Tilki B, Hurmuz P, et al. Stereotactic Radiotherapy to Oligoprogressive Lesions Detected With 68Ga-PSMA-PET/CT in Castration-Resistant Prostate Cancer Patients. *Eur J Nucl Med Mol Imaging* (2021) 48(11):3683–92. doi: 10.1007/s00259-021-05298-z
56. Deek MP, Taparra K, Phillips R, Velho PI, Gao RW, Deville C, et al. Metastasis-Directed Therapy Prolongs Efficacy of Systemic Therapy and Improves Clinical Outcomes in Oligoprogressive Castration-Resistant Prostate Cancer. *Eur Urol Oncol* (2021) 4(3):447–55. doi: 10.1016/j.euo.2020.05.004
57. Franzese C, Perrino M, Marzo MA, Badalamenti M, Baldaccini D, D'Agostino G, et al. Oligoprogressive Castration-Resistant Prostate Cancer Treated With Metastases-Directed Stereotactic Body Radiation Therapy: Predictive Factors for Patients' Selection. *Clin Exp Metastasis* (2022) 39(3):449–57. doi: 10.1007/s10585-022-10158-7
58. Berghen C, Joniau S, Ost P, Poels K, Everaerts W, Decaestecker K, et al. Progression-Directed Therapy for Oligoprogression in Castration-Refractory Prostate Cancer. *Eur Urol Oncol* (2021) 4(2):305–9. doi: 10.1016/j.euo.2019.08.012
59. Triggiani L, Mazzola R, Magrini SM, Ingrosso G, Borghetti P, Trippa F, et al. Metastasis-Directed Stereotactic Radiotherapy for Oligoprogressive Castration-Resistant Prostate Cancer: A Multicenter Study. *World J Urol* (2019) 37(12):2631–7. doi: 10.1007/s00345-019-02717-7
60. Triggiani L, Alongi F, Buglione M, Detti B, Santoni R, Bruni A, et al. Efficacy of Stereotactic Body Radiotherapy in Oligorecurrent and in Oligoprogressive Prostate Cancer: New Evidence From a Multicentric Study. *Br J Cancer.* (2017) 116(12):1520–5. doi: 10.1038/bjc.2017.103
61. University of Michigan Rogel Cancer Center. *FOcal Radiation for Oligometastatic Castration-Resistant Prostate Cancer (FORCE): A Phase II*

Randomized Trial (2021). Available at: https://clinicaltrials.gov/ct2/show/NCT03556904 (Accessed 2022 Apr 12).

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frontiers | Frontiers in Oncology

METHODS
published: 07 July 2022
doi: 10.3389/fonc.2022.888707

Multisite Radiotherapy Combined With Tislelizumab for Metastatic Castration-Resistant Prostate Cancer With Second-Line and Above Therapy Failure: Study Protocol for an Open-Label, Single-Arm, Phase Ib/II Study

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Background: Tislelizumab combined with radiotherapy as a salvage treatment for patients with end-stage metastatic castration-resistant prostate cancer (mCRPC) is not reported. This study aimed to describe a protocol to evaluate the safety and efficacy of multisite radiotherapy combined with tislelizumab as a salvage therapy for mCRPC in patients who had at least one second-line treatment failure.

Methods: The study included patients with mCRPC who had at least one lesion suitable for radiotherapy and failed androgen deprivation therapy (ADT), followed by at least one novel second-line endocrine therapy. All patients received tislelizumab monotherapy induction therapy for two cycles, then combined with multisite radiotherapy for one cycle, followed by tislelizumab maintenance therapy, until either disease progressed or the patient developed unacceptable toxicity. Radiation methods and lesions were individually selected according to the specified protocol. Primary endpoints included safety and objective response rate. Secondary endpoints included prostate-specific antigen (PSA) response rate, disease control rate, overall survival, radiographic progression-free survival (rPFS), and biochemical progression-free survival (bPFS). Furthermore, the exploratory endpoints included the identification of the predictive biomarkers and exploration of the correlation between biomarkers and the tumor response to the combined regimen.

Discussion: This study included three treatment stages to evaluate the efficacy of immunotherapy and the combination of immunotherapy and radiotherapy for patients with mCRPC who have had at least second-line treatment failure. Additionally, radiation-

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Edited by:
Constantinos Zamboglou, German Oncology Center, Cyprus

Reviewed by:
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Specialty section:
This article was submitted to Genitourinary Oncology, a section of the journal Frontiers in Oncology

Received: *03 March 2022*
Accepted: *10 June 2022*
Published: *07 July 2022*

Citation:
Cheng K, Wang Y, Chen Y, Zhu J, Qi X, Wang Y, Zou Y, Lu Q and Li Z (2022) Multisite Radiotherapy Combined With Tislelizumab for Metastatic Castration-Resistant Prostate Cancer With Second-Line and Above Therapy Failure: Study Protocol for an Open-Label, Single-Arm, Phase Ib/II Study. Front. Oncol. 12:888707. doi: 10.3389/fonc.2022.888707

related and immune-related early and late toxicities were determined, respectively. Furthermore, the study also aimed to identify the predictive biomarkers associated with immunotherapy for treating mCRPC.

Trial Registration: https://www.chictr.org.cn/showproj.aspx?proj=126359, identifier ChiCTR2100046212.

Keywords: metastatic castration-resistant prostate cancer (mCRPC), tislelizumab, PD-1 monoclonal antibodies, combination therapy, study protocol, multisite radiotherapy

INTRODUCTION

Prostate cancer (PCa) is the world's second leading cause of cancer-related mortality in men (1). China has the sixth-highest rate of incidence and mortality due to PCa (2). Androgen deprivation therapy (ADT) is one of the most important therapies for patients with hormone-sensitive PCa. Unfortunately, most patients with PCa eventually develop metastatic castration-resistant prostate cancer (mCRPC) within 2–3 years of undergoing ADT (3, 4). Currently, multiple approved therapies can prolong the survival of patients with mCPRC, including new-generation hormone drugs, such as abiraterone and enzalutamide, and chemotherapeutic drugs, such as docetaxel and cabazitaxel, targeted therapy drugs, and immunotherapy drugs (Sipuleucel-T) (5). However, despite the efficacy of these drugs, cancer cells inevitably develop resistance to them (6). Once patients fail the second-line endocrine therapy, there is a lack of a standard treatment model for subsequent treatments. A clinical trial suggested that a common subset of mCRPC, characterized by defects in DNA repair, could be treated using the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib in patients with mCRPC who had developed resistance to standard treatments (7, 8). However, this subset only accounted for approximately 11.8% of all sporadic mCRPC (2). Most patients could not achieve durable responses with available treatments. Thus, it was a fundamental requirement to identify novel strategies to improve the survival of patients with mCRPC after the failure of second-line endocrine therapy.

The introduction of immunotherapy-targeted programmed death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) has altered the treatment paradigm for various types of malignancies. Unfortunately, immunotherapy has only shown modest efficacy against PCa (9). As per the results of two recently published clinical studies, two anti-PD-1 antibodies, pembrolizumab and atezolizumab were well tolerated and safe in patients with mCRPC. However, complete response (CR) was achieved in only a few patients (10, 11). Tislelizumab, an investigational anti-PD-1 antibody, has been shown to be significantly efficacious in (85.7% objective response rate (ORR)) patients with relapsed/refractory classical Hodgkin's lymphoma (12). A recently published research demonstrated that tislelizumab showed substantial clinical benefits and an acceptable safety profile in patients with urothelial carcinoma (13). Another study found that tislelizumab had disease stabilization capacity for various tumor types and in patients who had undergone different types of long-term treatments (14). Thus, it was speculated that tislelizumab might act as an effective salvage treatment strategy to improve the outcomes in patients with mCRPC. However, due to the "cold tumor" characteristics of PCa, the response to immunotherapy in PCa might not be as strong compared with other tumors (1). Thus, a combination of immunotherapy and other current treatment strategies, such as chemotherapy, targeted therapy, and radiotherapy (RT), could improve the immune response to "cold tumors." Previous studies have reported that ipilimumab monotherapy or the addition of atezolizumab to enzalutamide for treating patients with mCRPC could not provide a satisfactory primary endpoint for overall survival (OS) (15, 16). However, using ipilimumab plus RT showed improved outcomes compared with placebo plus RT in patients with postdocetaxel mCRPC (17). Consequently, RT could be a promising strategy for the synergistic enhancement of immunotherapeutic efficacy.

Numerous clinical trials have supported the use of RT in the modification of antitumor immune responses, enhanced expression of antigens on the surface of tumor cells, as well as tumor antigen crosspresentation in the draining lymph nodes, directly resulting in the activation and proliferation of tumor-specific cytotoxic T cells (18–21). Consequently, this might result in a modified tumor microenvironment along with the expansion of immunotherapeutic capacity (22, 23). Multisite stereotactic body radiotherapy (SBRT) has emerged as an altering paradigm for treating solid metastatic tumors (24). A phase I study indicated that multisite SBRT combined with pembrolizumab for solid metastatic tumors was well tolerated with acceptable levels of toxicity (25). However, there is a scarcity of sufficient studies examining the therapeutic effects of combined anti-PD-1 and multisite SBRT in mCRPC treatment,

Abbreviations: mCRPC, metastatic castration-resistant prostate cancer; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; rPFS, progression-free survival; bPFS, biochemical progression-free survival; PCa, prostate cancer; PD-1, programmed death receptors; PD-L1, programmed death-ligand 1; CR, complete response; RT, radiotherapy; SBRT, stereotactic body radiotherapy; PD, disease progression; PCWG3, Prostate Cancer Working Group 3; OS, overall survival; IMRT, intension-modulated radiotherapy; CT, computed tomographic; ORR, objective response rate; PR, partial response; PSA, prostate-specific antigen; PFS, progression-free survival; SD, stable disease; AEs, adverse events; MMR, mismatch repair protein; AR-V7, androgen receptor splice variant 7; TIL, tumor-infiltrating lymphocyte; M1-TAM, antitumor M1-like; M2-TAM, protumor M2-like; TMB, tumor mutation burden; TC, T cell receptor; irAEs, immune-related adverse events; SAEs, serious adverse events; CTCAE, Common Toxicity Criteria for Adverse Events; NSCLC, nonsmall-cell lung cancer; ICD, immunogenic cell death; dMMR, mismatch repair deficiency; POLE, polymerase epsilon.

necessitating further research. Another phase II trial demonstrated that avelumab combined with SBRT exhibited elevated activity and acceptable toxicity in treatment-refractory mCRPC (26). Although a study reported that SBRT with a few fractionations was the best choice for the abscopal effect (27), an appropriate RT technique should be chosen based on the symptoms and condition of the patient with mCRPC. Previous studies have demonstrated that low-dose radiation (e.g., doses below 3 Gy) could promote immune cell infiltration into the stroma and the tumor bed of distant tumors, resulting in an improved rate of the systemic response to metastatic disease (28).

Furthermore, low-dose radiotherapy against established metastases has also been shown to significantly enhance the abscopal response to hypofractionated RT plus immune checkpoint inhibitors (29). Low-dose radiation also carries the potential to amplify the antitumor immune effects. Another study suggested that low-dose radiation (a maximum dose of 8–10 Gy/fraction) could induce interferon signaling, resulting in RT-induced abscopal outcomes (30). Several studies also indicated that multiple dose-fractionation schedules of RT resulted in an enhanced abscopal effect compared to a single dose (31, 32). However, further research is required to explore whether the reported doses of RT would exhibit the activation impact in combination with immunotherapy. Thus, combination trials of immunotherapy and RT could be designed to optimize the choice of optimal dose and fractionation.

Here, we aimed to analyze the safety and efficacy of multisite radiotherapy combined with tislelizumab for patients with mCRPC who have experienced failure of at least one second-line treatment. Additionally, we planned to explore the predictive biomarkers of the efficacy of this combined regimen to facilitate clinical studies.

MATERIALS AND METHODS

Study Design

This study is an open-label, single-arm, phase Ib/II prospective study including patients with mCRPC who experienced disease progression after treatment with ADT and had at least one second-line endocrine therapy failure (abiraterone acetate or enzalutamide). This study includes 48 patients, with the entire study (treatment and follow-up phases) lasting approximately 36 months; the maximum duration of tislelizumab treatment has been limited to 2 years. This study protocol has been approved by the Ethics Review Committee of West China Hospital, Sichuan University (Ethical approval number: 2021203). Written informed consent was obtained from all patients. The study has been registered on the Chinese Clinical Trials Registry (Chictr.org.cn) with registration number: ChiCTR2100046212.

Eligibility Criteria

All patients who conformed to the inclusion criteria were included (**Table 1**). Additionally, patients would be able to withdraw from the study if they experience progression of disease (PD), elevated levels of toxicities, are lost to follow-up, die, undergo protocol violation, concomitant disease, or based on the investigator's decision.

PD was assessed *via* imaging (CT/MRI/bone scan) as per Prostate Cancer Working Group 3 (PCWG3)–modified RECIST v1.1, a revised version in PCWG3 based on PCWG2.

Procedures

Figure 1 summarizes the execution outline of this study. Even if patients discontinue treatment due to disease progression, toxicity, or any other reason, they were followed up every 3 months after the end of treatment.

Screening

The enrolled patients were screened within 2 weeks of the initiation of treatment. The following necessary procedures were performed during the screening: a collection of demographic and medical history, physical examination, estimation of PS ECOG, diagnosis and staging of the primary tumor, laboratory examination (blood, liver, kidney, heart, and thyroid function examinations), and imaging analysis. Finally, enrolled patients were required to sign a written informed consent.

Treatment

Figure 2 shows the therapeutic scheme, which has been divided into three phases, including induction therapy (phase 1), combination therapy (phase 2), and maintenance therapy (phase 3).

In phase 1, patients received 1-h intravenous tislelizumab (provided by BeiGene, Beijing, China) at 200 mg every 3 weeks for two cycles. As described in **Table 2**, tislelizumab was suspended or terminated in the case of severe adverse events.

In phase 2, patients received tislelizumab combined with multisite RT for one cycle. During this phase, tislelizumab was administered at 200 mg once every 3 weeks; the schedule for multisite radiotherapy is presented in **Figure 2**. RT was performed using the intension-modulated radiotherapy (IMRT) technique under computed tomographic (CT) localization at 6MV-X rays. SBRT was recommended as the method of choice for RT.

The RT was administered to one or three disease sites, selected based on a prioritization order **(Table 3)**. **Table 3** also shows the preferred choice of radiotherapy doses/fractions for individual metastases. Furthermore, the exact dose/fraction might be limited by the paracancerous tissue sites in the patient. Thus, based on the actual condition of the patient, we also considered adopting the preferred dose/fraction of RT, as shown in **Figure 2**.

Lymph nodes with a short diameter ≥1 cm on CT were considered metastatic lymph nodes. Moreover, pelvic wall, retroperitoneal, mediastinum, clavicle, and axilla lymph nodes were preferentially selected as gross tumor volume of lymph nodes (GTVnd) for RT (**Figure 2**) and without prophylactic irradiation of the lymph node drainage area. **Table 4** shows normal tissue dose constraints (33).

Phase 3 was initiated 14 days after completing synchronous radiation, followed by tislelizumab maintenance therapy

TABLE 1 | The key inclusion and exclusion criteria of this study.

Inclusion criteria

1. Patients with incurable metastatic or unresectable prostate cancer, which was confirmed by histopathology and/or cytology (including postoperative recurrence and metastasis) without neuroendocrine differentiation or small cell features.
2. Patients who failed ADT therapy combined with at least one novel endocrine therapy (including enzalutamide, abiraterone, apalutamide, and so on, while not including bicalutamide and flutamide) or failed ADT therapy followed by at least one novel endocrine therapy.
3. Patients with hormone-sensitive prostate cancer (HSPC) who had not received ADT therapy combined with a docetaxel regimen, or patients who required or were unable to tolerate or refused docetaxel regimen chemotherapy after diagnosis of CRPC.
4. Patients with mCRPC with DNA-HRR gene mutation who had not received PARP inhibitor therapy, who had refused PARP inhibitor therapy, or had a contraindication to PARP inhibitor therapy.
5. Disease progression was recorded in patients (disease progression was defined as one or more of the following 3 events) in the 6 months prior to enrolment:
1. PSA progression: elevated PSA levels were measured at least thrice with an interval of ≥1 week, and the PSA value was expected to be ≥2 ng/ml each time.
2. For patients without PSA progression, imaging (RECIST 1.1) assessed the presence of soft tissue or bone metastatic lesion progression.
3. PCWG2-defined progression of bone lesions, i.e., two or more new lesions found on bone scan.
4. Patients with clinical evidence of distant metastatic disease (based on bone scan, CT/MRI).
5. For patients currently on continuous ADT therapy, serum total testosterone was required to be <50 ng/dl.
6. The ECOG PS ≤2.
7. Patients with expected survival time >6 months.
8. Patients with adequate organ and bone marrow function.
Laboratory tests should meet the following criteria:
1. Routine blood test: Hb ≥90 g/L (no blood transfusion within last 14 days); ANC ≥1.5 × 10^9/L; PLT ≥100 × 10^9/L
2. Biochemical tests: CR ≤1.5 × ULN or CRCL ≥60 mL/min when serum creatinine >1.5 × ULN of subjects; Bilirubin Bil ≤1.5 × ULN; ALT and AST ≤2.5 × ULN (subjects with liver metastasis ≤5 × ULN)
3. Coagulation function: the INR <1.5.
9. Reproductive men should use an appropriate method of contraception for a period of 120 days from the first study drug administration to the last study drug administration.

Exclusion criteria

1. Patients who had not recovered from the toxicity induced by the original treatment regimen and still had toxicity reactions >grade 1 before enrolment.
2. Patients who participated in clinical trials of other drugs within the last 1 month.
3. Patients who had been diagnosed with immunodeficiency or were receiving systemic steroid therapy or any other form of immunosuppressive therapy 7 days prior to study initiation. If patients had to receive systemic steroid therapy (e.g., prednisone) before the start of immunotherapy, the maximum allowed dose of prednisone was 10 mg/day, else they were excluded.
4. Patients who had used or were using a FAK inhibitor or anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug targeting the T-cell costimulatory or checkpoint pathway) within 4 weeks prior to study initiation.
5. Patients who had a history of other malignant tumors (except for basal cell carcinoma or orthotopic cervical cancer) within the last 5 years.
6. Patients with known or suspected new BMs: subjects with signs or symptoms suggestive of BMs were not allowed to participate in the study unless BMs had been ruled out by CT or MRI. However, subjects with controlled BMs (no radioactivity progression for at least 4 weeks after radiotherapy and/or no neurological symptoms or signs after surgical resection) were enrolled.
7. Patients who had an active autoimmune disease requiring systemic treatment (e.g., use of disease modifiers, corticosteroids, or immunosuppressive drugs) within the past 2 years.
8. Patients who had interstitial pulmonary disease and/or present (noninfectious) pneumonia requiring continued steroid therapy.
9. Patients who had combined active infection requiring systemic treatment.
10. Patients who had a history of epilepsy or were taking drugs that caused epilepsy or had a history of severe central nervous system diseases.
11. Patients who had severe cardiovascular disease, previous myocardial infarction or arterial thrombosis, unstable angina pectoris, or heart failure with clinical symptoms in the past 6 months.
12. Patients who had serious, uncontrolled medical disorders or active infections that could impair their ability to receive treatment as prescribed in the protocol, including but not limited to HIV positive and active tuberculosis.
13. Researchers considered the patients were inappropriate to participate.

ADT, androgen deprivation therapy; HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (ADP-ribose) polymerase; PSA, prostate-specific antigen; RECIST 1.1, Response Evaluation Criteria in Solid Tumors; PCWG2, Prostate Cancer Working Group; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Hb, hemoglobin; ANC, neutrophils absolute value; PLT, platelet; CR, serum creatinine; CRCL, creatinine clearance rate; AST, aspartate aminotransferase; INR, international standardized ratio; ULN, upper limit of normal; BMs, brain metastases; CT, computed tomography; MRI, magnetic resonance imaging; HIV, human immunodeficiency virus.

(200 mg; once every 3 weeks) until either the disease progressed or the patient developed unacceptable toxicity. However, notably, pseudoprogression might occur in the maintenance phase of tislelizumab, which would be required to be distinguished from actual progression by the researchers.

Study Endpoints and Assessment

The primary endpoints included safety and ORR. ORR is defined as the proportion of patients who achieved a CR or partial response (PR). Secondary endpoints included the following indicators: prostate-specific antigen (PSA) response rate (PCWG3), disease control rate (DCR), OS, and progression-free survival (PFS) (radiographic PFS (rPFS), biochemical PFS (bPFS)). Here, rPFS is the time between the initial treatment start and radiographic PD, and bPFS is the time between the start of initial treatment and PD (caused by continuous elevation of PSA). We defined the PSA response rate as a 50% decline in PSA levels from baseline to 12 weeks after receiving tislelizumab monotherapy and the DCR as the proportion of patients whose best response was CR, PR, or stable disease (SD).

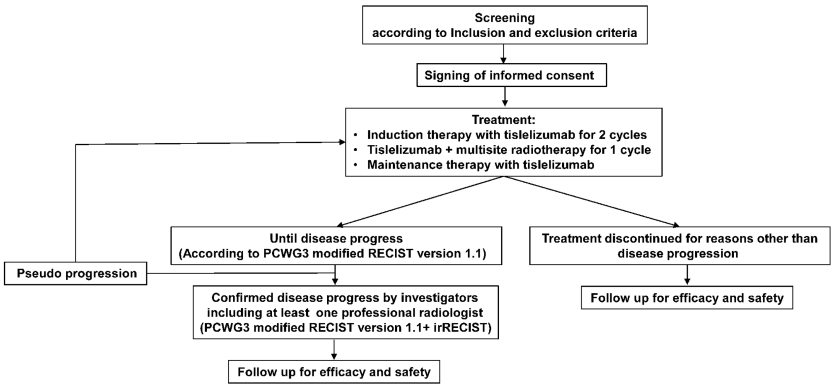

FIGURE 1 | Flowchart of this study. PCWG3, Prostate Cancer Working Group 3; RECIST version 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; irRECIST, Immune-related Response Evaluation Criteria in Solid Tumors.

PFS is the time interval between therapy initiation and radiographic or biochemical PD, or death, whichever comes first. Furthermore, the exploratory purpose of this study was to explore the predictive biomarkers as described in the **Discussion** and **Appendix Table 1** that were related to efficacy and survival, which would help guide toward more individualized therapy.

In this study, laboratory testing and imaging examination were used to evaluate clinical symptoms, tumor response, adverse events (AEs), and biomarkers (**Appendix Table 1**). A radiological review determined the tumor response every two treatment cycles (6 weeks). If disease progression was indicated based on imaging analysis, subsequent imaging analysis would be done to confirm this at least 4 weeks later. If pseudoprogression was confirmed, the investigator would then decide whether treatment could be continued.

The following data were recorded for safety and ORR assessment: demographics and medical history, physical examination, vital signs, laboratory testing, imaging examination, PSA, AEs, and biomarkers testing. The predictive biomarkers evaluated in this analysis included the following: the expression of DNA mismatch repair protein (MMR), androgen receptor splice variant 7 (AR-V7), tumor PD-L1, tumor-infiltrating lymphocyte (TIL) count, classification of immune cells and subsets ($CD4^+$T, $CD8^+$T, Treg, MDSC, M1-TAM

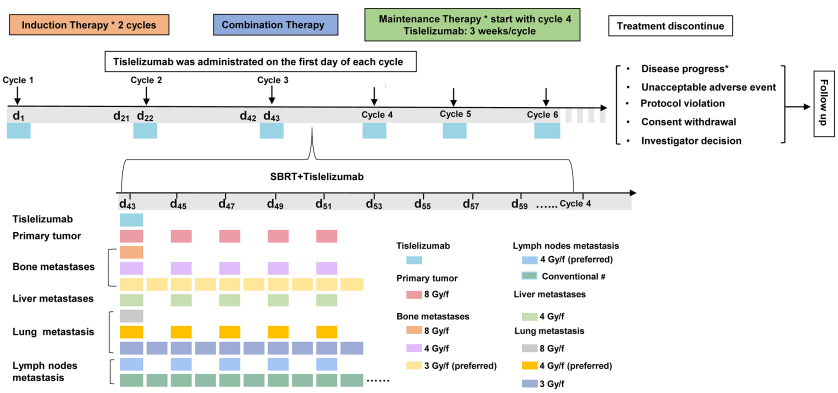

FIGURE 2 | Flowchart of the treatment protocol. The therapeutic scheme has been divided into four phases: Induction phase, where patients were scheduled to receive the tislelizumab every 3 weeks (21-day cycle) for two cycles; Combination phase, where patients were scheduled to receive the SBRT (once every 2 days during one cycle) combined with tislelizumab (on day 1 every cycle); and Consolidation and maintenance phases, at 14 days after completing synchronous radiation, where patients were scheduled to receive tislelizumab alone on day 1 of a 21-day cycle until treatment was discontinued. During the follow-up, observing this study's safety and clinical efficacy were observed. Abbreviations: PD-1, programmed cell death-1; SBRT, stereotactic body radiation therapy. The asterisk indicates that disease progression was confirmed according to the modified RECIST 1.1 of PCWG3. The number sign indicates that patients would receive conventional radiotherapy with 2 Gy every day up to a total dose of 40 or 50 Gy if the surrounding critical organs were at risk around lymph nodes, such as the duodenum, small intestine, and colon.

TABLE 2 | Dose adjustment protocol for tislelizumab.

Adverse events	Severity	Dose adjustment
Pneumonia	Grade 2 of pneumonia	Dose interruption[a]
	Recurrent grade 2 of pneumonia, grade 3/4 of pneumonia	Permanent discontinuation
Diarrhea/enterocolitis	Grade 2/3 of diarrhea or enterocolitis	Dose interruption[a]
	Grade 4 of diarrhea or enterocolitis	Permanent discontinuation
Dermatitis	Grade 3 of dermatitis	Dose interruption[a]
	Grade 4 of dermatitis	Permanent discontinuation
Hepatitis	Grade 2 AST, ALT, or TBIL was increased in patients with normal baseline ALT, AST, or TBI; patients with AST, ALT, or TBIL above 50% (achieve level 2 requirements) and the duration <7 days	Permanent discontinuation[a]
	Grade 3/4 AST, ALT, or TBIL was increased in patients with normal baseline ALT, AST, or TBI; patients with AST, ALT, or TBIL above 50% (achieve level 3/4 requirements) and the duration ≥7 days	Permanent discontinuation
Inflammatory of the pituitary gland	Grade 2 of the pituitary gland inflammatory	Dose interruption[b]
	Grade 3/4 of the pituitary gland inflammatory	Permanent discontinuation
Adrenocortical dysfunction	Grade 2 of the adrenocortical dysfunction	Dose interruption[b]
	Grade 3/4 of the adrenocortical dysfunction adrenocortical dysfunction	Permanent discontinuation
Hyperthyroidism	Grade 3/4 of the hyperthyroidism	Permanent discontinuation
Type I diabetes	Grade 3 of hyperglycemia	Dose interruption[b]
	Grade 4 of hyperglycemia	Permanent discontinuation
Renal insufficiency	Grade 2/3 CR increased	Dose interruption[a]
	Grade 4 CR increased	Permanent discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Dose interruption[a]
	Grade 3/4 neurotoxicity	Permanent discontinuation
Other AE	The first time occurs for other level 3 AEs	Dose interruption[b]
	The same level 3 AE occurs a second time	Permanent discontinuation
	Grade 3 AE cannot be reduced to baseline level for 0–2 within 7 days or returned to baseline level for 0–1 within 14 days	Permanent discontinuation
	Grade 4 AE	Permanent discontinuation[c]

The maximum duration of dose interruptions was 12 weeks. However, if patients were unable to tolerate tislelizumab, then it was permanently discontinued, and patients were followed, except for the following two conditions (1): Tislelizumab was interrupted for more than 12 weeks due to a dose reduction of glucocorticoids (glucocorticoid was used for immune-related AE treatment). The investigator and sponsor decided whether patients would continue to receive tislelizumab treatment. However, during dose interruption, the imaging tests, which were used for efficacy assessment, were conducted as planned (2). Tislelizumab was interrupted for more than 12 weeks due to treatment for AE that was unrelated to tislelizumab. The investigator and sponsor decided whether patients would continue to receive tislelizumab treatment. However, during dose interruption, the imaging tests, which were used for efficacy assessment, were conducted as planned. If the toxicity returned to grade ≤1 or baseline, and the ECOG PS ≤1, patients could continue to receive tislelizumab treatment. Notice that in the stage 1 study, if 14/29 patients stopped the treatment because of SAEs, the study was stopped early.

[a]*Dosing could be resumed once the symptoms improve to grade 0–1 or baseline.*

[b]*Dosing could be resumed for patients who had pituitary or adrenocortical insufficiency, hypothyroidism, and type 1 diabetes, once the diseases were adequately controlled using physiological hormones.*

[c]*Investigator decided to terminate medicine for abnormal results in grade 4.*

(antitumor M1-like), M2-TAM (protumor M2-like)), the status of homologous recombination repair gene, AR pathway-related genes, and tumor mutation burden (TMB) level in tumors. In addition, we would also determine the classification of immune cells and subsets and TMB levels in peripheral blood.

Follow-Up

Patients who successfully completed the interventional treatment were followed up for 30 days, and rAEs were recorded. In the case of no complications, patients were followed up every 2–3 months to collect antitumor treatment data and OS. However, patients who discontinued treatment for reasons other than PD were followed up every 8 weeks, followed up *via* imaging evaluation. If patients developed PD, they were followed up every 12 weeks to collect OS until death, consent to withdrawal, or the end of the study.

Safety

During safety evaluation, we observed and recorded all AEs (including acute and late radiotherapy-related adverse events, immune-related adverse events (irAEs)), serious adverse events (SAEs), laboratory examination, general physical examination, performance status score, electrocardiogram, echocardiogram, thyroid function, myocardial markers, etc. The Common Toxicity Criteria for Adverse Events (CTCAE) v4.0 were used to classify AEs. Additionally, the radiation toxicity criteria of the

TABLE 3 | The priority order for the selection of disease sites.

Lesions	Prioritization	Preferred dose/fraction	Alternative dose fraction schedules
Primary lesions[a]	1	8 Gy/f	NA
Symptomatic vertebral lesions or symptomatic lesions adjacent to the spinal cord[b]	2	3 Gy/10f	8 Gy/f or 4Gy/5f
Vertebral body or disc metastasis lesions associated with the spinal cord or adjacent to the spinal cord	3	3 Gy/10f	8 Gy/f or 4Gy/5f
Symptomatic nonspinal bone metastatic lesions[c]	4	3 Gy/10f	8 Gy/f or 4Gy/5f
Lymph node lesion (patients with symptoms of compression)	5	4 Gy/5f	Conventional fractionation
Lymph node lesion (patients with no symptoms of compression)	6	4 Gy/5f	Conventional fractionation
Asymptomatic bone metastasis lesions	7	4 Gy/5f	8 Gy/f or 3 Gy/10f
Liver metastasis lesions	8	4 Gy/5f	NA
Lung metastasis lesions	9	4 Gy/5f	8 Gy/f or 3 Gy/10f
Other	10	According to the choice of the investigator and radiologist	According to the choice of the investigator and radiologist

The maximum number of metastases (per patient and/or per organ system) allowed for being eligible for the study was three disease sites. The disease sites were selected according to this prioritization order.

[a]In patients who did not receive treatment via radical prostatectomy and RT for the primary tumor, the primary lesions were given priority to receive RT.

[b]Patients who had pain in the vertebral section or disc metastasis lesions that were caused by spinal cord compression or adjacent to the spinal cord.

[c]Patients had pain due to nonspinal bone metastatic lesions that were caused by nonspinal cord compression (including thigh pain, scapula pain, etc.).

Although the dose/fraction of RT in this table was the preferred choice for disease sites, the exact dose/fraction was limited by the paracancerous tissues of the patient. Thus, according to the patient's actual conditions, we also considered adopting the optional dose/fraction of RT in ***Figure 2****.*

Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) guidelines were used to assess the acute and late radiotherapy-related toxicities of grade and management (34). Secondly, the irAEs were also graded and managed according to the updated ASCO guidelines (35). Additionally, the "early" (<12 months) and "late" (>12 months) irAEs were categorized based on recent research data (36, 37). In this study, the following SAEs were considered: death, life-threatening AEs, in-patient or prolongation of existing hospitalization, permanent/severe disability, congenital anomalies/birth defects, or any significant medical event requiring intervention. Any AEs were registered during the AE reporting period. In addition, AEs associated with the investigational drug were also registered after reporting. All patients exhibiting SAEs were discontinued immediately, and the investigator reported cases to the sponsor as well as the ethics committee of the hospital within 24 h.

TABLE 4 | Normal tissue dose constraints for stereotactic radiotherapy.

Description	Constraint	5 fractions (Gy)	
		Optimal	Mandatory
Heart	DMax (0.5 cm^3)	<27	<27
Lungs	V20 Gy	–	<10%
Duodenum	DMax (0.5 cm^3)	–	<35
	D10 cm^3	–	<25
Stomach	DMax (0.5 cm^3)	<33	<35
	D10 cm^3	–	<25
Small bowel	DMax (0.5 cm^3)	<30	<35
	D10 cm^3	–	<25
Rectum	DMax (0.5 cm^3)	–	<32
Liver	V10 Gy	<70%	–
Kidneys	Mean dose	<10	–
Bladder	D15 cm^3	–	<18.3
	DMax (0.5 cm^3)	–	<38
Brainstem (not medulla)	DMax (0.1 cm^3)	<23	<31
Brain	D10 cm^3	–	–

Normal tissue dose constraints were referred to as the "UK consensus on normal tissue dose constraints for stereotactic radiotherapy."

DMax is the near-point maximum dose, referred to as D0.1 cm^3 or D0.5 cm^3, which was the minimum dose to the 0.1- or 0.5-cm^3 volume of the organ receiving the highest doses; D10 cm^3 and D15 cm^3 were the minimum doses to the specified volume of the organ (10 or 15 cm^3) that received the highest doses; V10 Gy or V20 Gy was the percentage volume of the organ receiving a dose of 10 or 20 Gy or higher.

Statistical Analysis

The sample size of this study was calculated according to Simon's two-stage method (α = 0.05 (bilateral), β = 0.2) and by using efficacy as the estimation index. In a previous KEYNOTE-199 study, ORR was reported to be 5% in 133 patients who were PD-L1 positive in cohort 1 and 3% in 66 patients who were PD-L1 negative in cohort 2. The response rate of these 199 patients in the two cohorts was 4.5% (10). In this study, we hypothesized that the effective rate of radiotherapy combined with tislelizumab would reach 15%. Thus, 48 patients were enrolled and divided into two stages. A stage 1 study included 29 patients; stage 2 consisted of 15 patients when the ORR from stage 1 reached at least 1 (RECIST v1.1). Four patients were then added, considering a 10% loss to follow-up or dropout rate.

The primary efficiency analysis will be performed on the complete analysis set, including all subjects assigned to interventional therapy. Patients who received ≥1 dose of the investigational drug and recorded safety indicators were evaluated for safety analysis. Descriptive statistics were provided using medians (ranges) and means (standard deviations) for continuous variables and frequency (proportions) for categorical variables. The Clopper–Pearson method was used for PSA response rates and 95% CI. The Kaplan–Meier method was used to estimate the PFS and OS; the median values were estimated with a 95% CI. All statistical analyses were two-sided, and $p < 0.05$ was considered significant. All statistical analyses were done using SPSS software v25.0.

Data Collection and Management

All researchers in this study were responsible for the accuracy of the collected data as well as data management. The data monitoring committee (DMC) conducted regular data monitoring during and after the study.

DISCUSSION

This study presents the first investigational analysis of the safety and efficacy of tislelizumab combined multisite RT for patients with mCRPC who had experienced failed ADT and at least one second-line endocrine therapy failure. Until now, the poor responses of immunotherapy against PCa might be attributed to its characteristics of low immune infiltration, low tumor mutation load, and low antigen presentation (38). Additionally, PCa evades and inhibits antitumor immunity *via* elevated expression of PD-L1 and enrichment of Tregs in both tumor and peripheral blood [19-21]. Interestingly, various studies have confirmed that a combination of immunotherapy and RT could constitute a promising strategy for the synergistic enhancement of treatment efficacy. In the last few years, several studies on various types of tumors have explored the combination of radiotherapy and immunotherapy, such as breast cancer, melanoma, nonsmall-cell lung cancer (NSCLC), and esophageal squamous cell carcinoma (39). All studies showed promising antitumor activity and acceptable tolerability. In recent years, there have been significant advances in the treatment of PCa, and several new treatment strategies for mCRPC with clinically proven survival benefits for mCRPC have been developed (10, 11, 40). However, there is still a lack of appropriate strategies for patients with mCRPC who have experienced ADT failure and second-line endocrine therapy. A recent study revealed that avelumab with SABR showed promising activity and acceptable toxicity in treatment-refractory mCRPC (26), indicating that immunotherapy combined with RT was still the best area of research. However, the data were limited to only one combination of tislelizumab and RT, limiting the treatment potential of mCRPC. Therefore, the combination treatment of tislelizumab plus multisite radiotherapy represents a potential approach and needs further investigation for patients with mCRPC who had experienced failure of ADT and second-line endocrine therapy.

The present study has been designed for three treatment phases. Tislelizumab monotherapy aims to observe the efficacy of tislelizumab monotherapy for patients with mCRPC by measuring changes in patients' PSA levels and symptoms. Due to the "cold tumor" characteristics of PCa, we predict that the 2-cycle efficacy of tislelizumab monotherapy may be insignificant. But it may show effectiveness in some patients who might benefit from immunotherapy in a short period, and those patients are worth being screened for biomarkers for immunomonotherapy.

Some patients with an immediate immune reaction to immunotherapy may result in irAEs. Previous studies reported that patients who experienced irAEs demonstrated marked improvements in immunotherapy efficacy compared to those with low toxicity (41). However, if irAEs occur prematurely (≤8 weeks), immunotherapy is likely to be discontinued due to toxicity. Therefore, we designed two cycles of tislelizumab monotherapy. Furthermore, recent retrospective studies have indicated that "early" irAEs were associated with poor prognosis, and the immunosuppressive treatment for irAEs may hinder anti–PD-1 monotherapy efficacy (42, 43). Therefore, the monotherapy phase would also help understand whether the early irAEs will occur in tislelizumab monotherapy, thus assessing the safety of tislelizumab monotherapy. Followed by the tislelizumab combined RT, comparing the efficacy and safety of tislelizumab monotherapy, the safety and synergistic effect of multisite RT combined with immunotherapy can be better observed. Furthermore, the safety and efficacy of RT can still be fully observed due to a delayed effect from RT, even if entering the tislelizumab monotherapy maintenance phase. Notably, suppose patients with mCRPC obtain a good survival benefit from this study, then the treatment value of tislelizumab as a maintenance therapy method in these patients could obtain preliminary verification.

Until now, there has been a lack of consensus regarding the ideal dose of RT in combination with immunotherapy. SBRT, as a novel RT method, is essential in the treatment of early primary cancer and oligometastatic disease, such as oligometastatic (≤5 lesions) PCa, early-stage nonsmall-cell lung cancer, and liver cancer (44, 45). It has the potential to deliver a small amount of ultra-high doses of radiation to relatively small target lesions, achieving local control with a low risk of toxicity (46). For advanced cancer patients with multiple metastases, the dose of irradiated lesions might be different to achieve excellent local control with a low risk of toxicity and more potent immune activation effects. Therefore, individualized RT will be performed in this study. We will still preferentially select treatment with SBRT, 40 Gy in five fractions, every other day for primary lesions.

On the one hand, the hypofractionated SBRT regimen of 40 Gy/5 is delivered to accommodate the radiation tolerance of organs at risk. On the other hand, the hypofractionated SBRT regimen facilitates immunogenic cell death (ICD), leading to the release of tumor antigens, thus amplifying the efficacy of immunotherapy (47). However, the majority of patients with PCa usually present with multiple distant metastases. In such cases, the dose regimens, guidelines, and normal tissue constraints determined in carefully conducted, high-quality prospective trials should be adopted (44). According to the ASTRO guidelines and the SABR-COMET study (48), 30 Gy in 10 fractions was preferred to treat bone metastases in the present study, which plays a role in palliative pain relief and modulates the immune response microenvironment (49). For liver metastases, 20 Gy in 5 fractions was standard institutional practice. According to the 2011 consensus guidelines, the radiation dose fractionation for lung metastases mainly included 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions (50), and 20 Gy in 5 fractions was preferred for the treatment of bone metastases in the present study.

Furthermore, the present study combined immunotherapy treatment for patients with mCRPC who had failed multiline therapy and had a relatively long survival time. Thus, irAEs are

important safety parameters to consider, especially for fatal irAEs such as pneumonitis, neurologic toxicity, colitis/diarrhea, and hepatitis (51) as the significant life-threatening factors for elderly patients. Using the combination of higher radiation doses with anti-PD-1 immunotherapy may cause irAEs to occur in the long term. Therefore, SBRT with relatively low radiation doses was performed based on security considerations in this study.

Tislelizumab is a novel IgG4 anti-PD-1 mAb monoclonal antibody that minimizes binding to FcγR on the surface of macrophages to eliminate antibody-dependent phagocytosis, resulting in a higher affinity for PD-1 compared with pembrolizumab and nivolumab (12). Both clinical literature and pharmacokinetics (PK) analysis have demonstrated that tislelizumab is well tolerated for multiple advanced tumor types and supports fixed dosing (200 mg) (52). Therefore, in the present study, we used a fixed-dose instead of dose-escalation exploration, which avoided the uncertainty caused by dose exploration and improved the effectiveness of this study.

Additionally, the most important aim was to maximize the therapeutic benefits by developing predictive biomarkers of immunotherapy responsiveness. Several biomarkers have been associated with the treatment effect of anti-PD-1 therapy, such as TMB, mismatch repair deficiency (dMMR), PD-1 expression, and TIL number (53). At the same time, these have been reported to be relatively rare in patients with mCRPC. TMB, a biomarker independent of PD-L1 expression, has been revealed to have a significant association with ORR across multiple cancer types (54). However, the application of TMB in mCRPC needs further validation. A previous study suggested that tumors with dMMR are susceptible to PD-1 and PD-L1 inhibitors.

Meanwhile, dMMR tumors exhibit a dense infiltration of CD^{8+} TILs that have been shown to induce a better and more durable response (55). Several clinical studies have indicated the association between dMMR and immunotherapy-related responses and better prognosis in other solid tumors (55–57). However, this correlation needs further exploration in mCRPC. Numerous clinical trials have investigated that PD-L1 expression is the most widely adopted predictor, and high PD-L1 expression is associated with clinical benefit and response rate improvement in anti-PD-1/anti-PD-L1 therapy (53). TIL is a vital component that influences the tumor immune microenvironment and is used for the prediction of immunotherapy combined with the expression of PD-L1 expression. Elevated levels of baseline TIL and PD-L1 expression in breast cancers were found to be associated with an increased probability of pathologic complete response (58). However, in the immunotherapy combination of multisite RT for mCRPC treatment, the predictive value of PD-L1 expression and TIL counts is vague and deserves further investigation.

Furthermore, studies have demonstrated that genomic alterations might elicit a broad impact on the tumor microenvironment, contributing to the promotion and maintenance of responses to immunotherapy (59–61). Thus, a genomic analysis needs to be performed in this study to determine the impact of genomic alterations (such as mutations in the exonuclease domain of the DNA polymerase epsilon (POLE), high tumor mutational burden, and the presence of biallelic loss of CDK12, among others) on immunotherapy for PCa, for the early detection and identification of novel therapeutic targets. Thus, it would be crucial to establish a comprehensive assessment framework involving multiple biomarkers for interrogating the tumor immune landscape and selecting sensitive patients.

However, this study has several limitations. It is a nonrandomized study with a small sample size. Therefore, the results of this study would provide preliminary support for future randomized, controlled trials to assess the combined therapeutic regimen for patients with mCRPC.

Thus, this study is the first attempt to evaluate the efficacy and safety of tislelizumab with multisite radiotherapy for patients with mCRPC who have failed ADT and second-line endocrine therapy, in an attempt to provide an accurate and effective combined treatment for patients with mCRPC and improve the survival status of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Review Committee of West China Hospital, Sichuan University (Ethical approval number: 2021203). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KC, YQW, YC, YCW, and ZL were involved in the study conception and design. ZL provided administrative support. KC, YQW, and YC provided materials and samples. KC, JZ, and XQ participated in data collection. KC, YQW, YC, YCW, ZL, JZ, and XH contributed to analysis and interpretation of the data and wrote the manuscript. All authors were involved in the final approval of the manuscript. All authors agreed to be accountable for all aspects of the work and approved the final manuscript.

FUNDING

This study was partly supported by the Sichuan Science and Technology Department Key Research and Development Project (22YFS0336) and 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYJC18048).

ACKNOWLEDGMENTS

Thanks are due to all the patients in our study and their family members. Thanks to Beigene for providing the study medication to the patients during the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.888707/full#supplementary-material

Supplementary Table 1 | Assessment timetable. In peripheral blood, the biomarkers and the main detection techniques included immune cells and subsets, such as $CD^{4+}T/CD^{8+}T$/Treg/MDSC/M1-TAM/M2-TAM (FCM); TMB (NGS). *PSA*, prostate-specific antigen; *AEs*, adverse events; *SAEs*, serious adverse events; *MMR*, mismatch repair protein; *PD-1*, programmed death-1; *PD-L1*, programmed death-ligand 1; *PD-L2*, programmed death-ligand 2; *TILs*, tumor-infiltrating lymphocytes; *MDSCs*, myeloid-derived suppressor cells; *M1-TAM*, antitumor M1-like; *M2-TAM*, protumor M2-like; *LAG-3*, lymphocyte activation gene 3; *TIM-3*, T-cell immunoglobulin mucin-3; *AR-V7*, androgen receptor variant 7; *TMB*, tumor mutation burden. Biomarker detection techniques: *IHC*, immunohistochemical; *HE staining*, hematoxylin-eosin staining; *FCM*, flow cytometry; *RNA-seq*, RNA sequencing. [a]In a tumor, the biomarkers and the main detection techniques were as follows: MMR (IHC), PD-1/PD-L1/PD-L2 (IHC), TIL (HE staining and IHC), immune cells, and subsets, such as $CD^{4+}T/CD^{8+}T$/Treg/MDSC/M1-TAM/M2-TAM (FCM); costimulatory factor: LAG-3/TIM-3/CD28/CD80/CD137 (GenecastPlex-59 panel), AR-V7 (IHC and NGS), homologous recombination repair genes (NGS), AR pathway-related genes (NGS), and RNA (RNA-seq).

REFERENCES

1. Baciarello G, Gizzi M, Fizazi K. Advancing Therapies in Metastatic Castration-Resistant Prostate Cancer. *Expert Opin Pharmacother* (2018) 19 (16):1797–804. doi: 10.1080/14656566.2018.1527312
2. Pritchard CC, Mateo J, Walsh MF, De Sarkar N, Abida W, Beltran H, et al. Inherited DNA-Repair Gene Mutations in Men With Metastatic Prostate Cancer. *New Engl J Med* (2016) 375(5):443–53. doi: 10.1056/NEJMoa1603144
3. Fizazi K, Jenkins C, Tannock IF. Should Docetaxel be Standard of Care for Patients With Metastatic Hormone-Sensitive Prostate Cancer? Pro and Contra. *Ann Oncol Off J Eur Soc Med Oncol* (2015) 26(8):1660–7. doi: 10.1093/annonc/mdv245
4. Gravis G, Boher JM, Joly F, Soulie M, Albiges L, Priou F, et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non Castrate Prostate Cancer: Impact of Metastatic Burden and Long-Term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. *Eur Urol* (2016) 70(2):256–62. doi: 10.1016/j.eururo.2015.11.005
5. Mao Y, Hu M, Yang G, Gao E, Chen W. Current Status of Castration-Resistant Prostate Cancer Drug Therapy. *Int J Surg: Oncol* (2021) 6(1):41–9. doi: 10.29337/ijsonco.126.
6. Alva A, Hussain M. Optimal Pharmacotherapeutic Management of Hormone-Sensitive Metastatic Prostate Cancer. *Drugs* (2013) 73(14):1517–24. doi: 10.1007/s40265-013-0106-3
7. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med* (2015) 373(18):1697–708. doi: 10.1056/NEJMoa1506859
8. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *New Engl J Med* (2020) 382 (22):2091–102. doi: 10.1056/NEJMoa1911440
9. Bansal D, Reimers MA, Knoche EM, Pachynski RK. Immunotherapy and Immunotherapy Combinations in Metastatic Castration-Resistant Prostate Cancer. *Cancers* (2021) 13(2):334. doi: 10.3390/cancers13020334
10. Antonarakis ES, Piulats JM, Gross-Goupil M, Goh J, Ojamaa K, Hoimes CJ, et al. Pembrolizumab for Treatment-Refractory Metastatic Castration-Resistant Prostate Cancer: Multicohort, Open-Label Phase II KEYNOTE-199 Study. *J Clin Oncol Off J Am Soc Clin Oncol* (2020) 38(5):395–405. doi: 10.1200/JCO.19.01638
11. Petrylak DP, Loriot Y, Shaffer DR, Braiteh F, Powderly J. Safety and Clinical Activity of Atezolizumab in Patients With Metastatic Castration-Resistant Prostate Cancer: A Phase I Study. *Clin Cancer Res* (2021) 27(12):3360–9. doi: 10.1158/1078-0432.ccr-20-1981
12. Song Y, Gao Q, Fan L, Zou D, Zhang H, Zhou J, et al. Tumor Microenvironment Associated With Complete Response to Tislelizumab Monotherapy in Relapsed/Refractory Classical Hodgkin Lymphoma Reveals a Potentially Different Mechanism of Action. *Blood* (2020) 136:17. doi: 10.1182/blood-2020-136696
13. Ye D, Liu J, Zhou A, Zou Q, Li H, Fu C, et al. Tislelizumab in Asian Patients With Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma. *Cancer Sci* (2021) 112(1):305–13. doi: 10.1111/cas.14681
14. Shen L, Guo J, Zhang Q, Pan H, Yuan Y, Bai Y, et al. Tislelizumab in Chinese Patients With Advanced Solid Tumors: An Open-Label, non-Comparative, Phase 1/2 Study. *J Immunother Cancer* (2020) 8(1):e000437. doi: 10.1136/jitc-2019-000437
15. Beer TM, Kwon ED, Drake CG, Fizazi K, Logothetis C, Gravis G, et al. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. *J Clin Oncol Off J Am Soc Clin Oncol* (2017) 35(1):40–7. doi: 10.1200/jco.2016.69.1584
16. Powles T, Yuen KC, Gillessen S, Kadel EE3, Rathkopf D, Matsubara N, et al. Atezolizumab With Enzalutamide Versus Enzalutamide Alone in Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase 3 Trial. *Nat Med* (2022) 28(1):144–53. doi: 10.1038/s41591-021-01600-6
17. Fizazi K, Drake CG, Beer TM, Kwon ED, Scher HI, Gerritsen WR, et al. Final Analysis of the Ipilimumab Versus Placebo Following Radiotherapy Phase III Trial in Postdocetaxel Metastatic Castration-Resistant Prostate Cancer Identifies an Excess of Long-Term Survivors. *Eur Urol* (2020) 78(6):822–30. doi: 10.1016/j.eururo.2020.07.032
18. Garnett CT, Palena C, Chakraborty M, Tsang KY, Schlom J, Hodge JW. Sublethal Irradiation of Human Tumor Cells Modulates Phenotype Resulting in Enhanced Killing by Cytotoxic T Lymphocytes. *Cancer Res* (2004) 64 (21):7985–94. doi: 10.1158/0008-5472.CAN-04-1525
19. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses *via* Cross-Presentation of Tumor Antigen. *Cancer Immunol Res* (2015) 3(4):345–55. doi: 10.1158/2326-6066.CIR-14-0196
20. Bernstein MB, Garnett CT, Zhang H, Velcich A, Wattenberg MM, Gameiro SR, et al. Radiation-Induced Modulation of Costimulatory and Coinhibitory T-Cell Signaling Molecules on Human Prostate Carcinoma Cells Promotes Productive Antitumor Immune Interactions. *Cancer biother radiopharmaceuticals* (2014) 29(4):153–61. doi: 10.1089/cbr.2013.1578
21. Sharabi AB, Tran PT, Lim M, Drake CG, Deweese TL. Stereotactic Radiation Therapy Combined With Immunotherapy: Augmenting the Role of Radiation in Local and Systemic Treatment. *Oncol (Williston Park NY)* (2015) 29 (5):331–40.
22. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC. *New Engl J Med* (2018) 379(24):2342–50. doi: 10.1056/NEJMoa1809697
23. Deng L, Liang H, Burnette B, Weicheslbaum RR, Fu YX. Radiation and Anti-PD-L1 Antibody Combinatorial Therapy Induces T Cell-Mediated Depletion of Myeloid-Derived Suppressor Cells and Tumor Regression. *Oncoimmunology* (2014) 3:e28499. doi: 10.4161/onci.28499
24. Zhang JY, Yan YY, Li JJ, Adhikari R, Fu LW. PD-1/PD-L1 Based Combinational Cancer Therapy: Icing on the Cake. *Front Pharmacol* (2020) 11:722. doi: 10.3389/fphar.2020.00722
25. Luke JJ, Lemons JM, Karrison TG, Pitroda SP, Melotek JM, Zha Y, et al. Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body

Radiotherapy in Patients With Advanced Solid Tumors. *J Clin Oncol Off J Am Soc Clin Oncol* (2018) 36(16):1611–8. doi: 10.1200/JCO.2017.76.2229
26. Kwan EM, Spain L, Anton A, Gan CL, Garrett L, Chang D, et al. Avelumab Combined With Stereotactic Ablative Body Radiotherapy in Metastatic Castration-Resistant Prostate Cancer: The Phase 2 ICE-PAC Clinical Trial. *Eur Urol* (2021) 81(3):253–62. doi: 10.1016/j.eururo.2021.08.011
27. Ashrafizadeh M, Farhood B, Eleojo Musa A, Taeb S, Rezaeyan A, Najafi M. Abscopal Effect in Radioimmunotherapy. *Int Immunopharmacol* (2020) 85:106663. doi: 10.1016/j.intimp.2020.106663
28. Herrera FG, Romero P, Coukos G. Lighting Up the Tumor Fire With Low-Dose Irradiation. *Trends Immunol* (2022) 43(3):173–9. doi: 10.1016/j.it.2022.01.006
29. Yin L, Xue J, Li R, Zhou L, Deng L, Chen L, et al. Effect of Low-Dose Radiation Therapy on Abscopal Responses to Hypofractionated Radiation Therapy and Anti-PD1 in Mice and Patients With Non-Small Cell Lung Cancer. *Int J Radiat oncol biol Phys* (2020) 108(1):212–24. doi: 10.1016/j.ijrobp.2020.05.002
30. Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ. DNA Exonuclease Trex1 Regulates Radiotherapy-Induced Tumour Immunogenicity. *Nat Commun* (2017) 8:15618. doi: 10.1038/ncomms15618
31. Theelen WS, de Jong MC, Baas P. Synergizing Systemic Responses by Combining Immunotherapy With Radiotherapy in Metastatic non-Small Cell Lung Cancer: The Potential of the Abscopal Effect. *Lung Cancer (Amsterdam Netherlands)* (2020) 142:106–13. doi: 10.1016/j.lungcan.2020.02.015
32. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated But Not Single-Dose Radiotherapy Induces an Immune-Mediated Abscopal Effect When Combined With Anti-CTLA-4 Antibody. *Clin Cancer Res an Off J Am Assoc Cancer Res* (2009) 15 (17):5379–88. doi: 10.1158/1078-0432.CCR-09-0265
33. Hanna GG, Murray L, Patel R, Jain S, Aitken KL, Franks KN, et al. UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy. *Clin Oncol (Royal Coll Radiologists (Great Britain))* (2018) 30(1):5–14. doi: 10.1016/j.clon.2017.09.007
34. Cox JD, Stetz J, Pajak TF. Toxicity Criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat oncol biol Phys* (1995) 31(5):1341–6. doi: 10.1016/0360-3016(95)00060-C
35. Schneider BJ, Naidoo J. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. *J Clin Oncol* (2021) 39(36):4073–126. doi: 10.1200/jco.21.01440
36. Ghisoni E, Wicky A, Bouchaab H, Imbimbo M, Delyon J, Gautron Moura B, et al. Late-Onset and Long-Lasting Immune-Related Adverse Events From Immune Checkpoint-Inhibitors: An Overlooked Aspect in Immunotherapy. *Eur J Cancer (Oxford Engl 1990)* (2021) 149:153–64. doi: 10.1016/j.ejca.2021.03.010
37. Nigro O, Pinotti G, De Galitiis F, Di Pietro FR, Giusti R, Filetti M, et al. Late Immune-Related Adverse Events in Long-Term Responders to PD-1/PD-L1 Checkpoint Inhibitors: A Multicentre Study. *Eur J Cancer (Oxford Engl 1990)* (2020) 134:19–28. doi: 10.1016/j.ejca.2020.04.025
38. Liu C, Wang M. Immune Checkpoint Inhibitor Therapy for Bone Metastases: Specific Microenvironment and Current Situation. *J Immunol Res* (2021) 2021:8970173. doi: 10.1155/2021/8970173
39. Cushman TR, Caetano MS, Welsh JW, Verma V. Overview of Ongoing Clinical Trials Investigating Combined Radiotherapy and Immunotherapy. *Immunotherapy* (2018) 10(10):851–0. doi: 10.2217/imt-2018-0019
40. Nuhn P, De Bono JS, Fizazi K, Freedland SJ, Grilli M, Kantoff PW, et al. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-Resistant Prostate Cancer in the Era of Precision Oncology. *Eur Urol* (2019) 75(1):88–99. doi: 10.1016/j.eururo.2018.03.028
41. Das S, Johnson DB. Immune-Related Adverse Events and Antitumor Efficacy of Immune Checkpoint Inhibitors. *J immunother Cancer* (2019) 7(1):306. doi: 10.1186/s40425-019-0805-8
42. Bai X, Hu J, Betof Warner A. Early Use of High-Dose Glucocorticoid for the Management of irAE Is Associated With Poorer Survival in Patients With Advanced Melanoma Treated With Anti-PD-1 Monotherapy. *Clin Cancer Res* (2021) 27(21):5993–6000. doi: 10.1158/1078-0432.ccr-21-1283
43. Maslov DV, Tawagi K, Kc M, Simenson V, Yuan H, Parent C, et al. Timing of Steroid Initiation and Response Rates to Immune Checkpoint Inhibitors in Metastatic Cancer. *J immunother Cancer* (2021) 9(7):e002261. doi: 10.1136/jitc-2020-002261
44. Lo SS, Fakiris AJ, Chang EL, Mayr NA, Wang JZ, Papiez L, et al. Stereotactic Body Radiation Therapy: A Novel Treatment Modality. *Nat Rev Clin Oncol* (2010) 7(1):44–54. doi: 10.1038/nrclinonc.2009.188
45. Ahmed KA, Barney BM, Davis BJ, Park SS, Kwon ED, Olivier KR. Stereotactic Body Radiation Therapy in the Treatment of Oligometastatic Prostate Cancer. *Front Oncol* (2012) 2:215. doi: 10.3389/fonc.2012.00215
46. Chen Y, Gao M, Huang Z, Yu J, Meng X. SBRT Combined With PD-1/PD-L1 Inhibitors in NSCLC Treatment: A Focus on the Mechanisms, Advances, and Future Challenges. *J Hematol Oncol* (2020) 13(1):105. doi: 10.1186/s13045-020-00940-z
47. Demaria S, Guha C, Schoenfeld J, Morris Z, Monjazeb A, Sikora A, et al. Radiation Dose and Fraction in Immunotherapy: One-Size Regimen Does Not Fit All Settings, So How Does One Choose? *J Immunother Cancer* (2021) 9(4): e002038. doi: 10.1136/jitc-2020-002038
48. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial. *J Clin Oncol Off J Am Soc Clin Oncol* (2020) 38(25):2830–8. doi: 10.1200/JCO.20.00818
49. Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich SE, et al. Palliative Radiation Therapy for Bone Metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* (2017) 7(1):4–12. doi: 10.1016/j.prro.2016.08.001
50. Rodrigues G, Videtic GM, Sur R, Bezjak A, Bradley J, Hahn CA, et al. Palliative Thoracic Radiotherapy in Lung Cancer: An American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. *Pract Radiat Oncol* (2011) 1(2):60–71. doi: 10.1016/j.prro.2011.01.005
51. Kennedy LB, Salama AKS. A Review of Cancer Immunotherapy Toxicity. *CA: Cancer J Clin* (2020) 70(2):86–104. doi: 10.3322/caac.21596
52. Desai J, Deva S, Lee JS, Lin CC, Yen CJ, Chao Y, et al. Phase IA/IB Study of Single-Agent Tislelizumab, an Investigational Anti-PD-1 Antibody, in Solid Tumors. *J immunother Cancer* (2020) 8(1):e000453. doi: 10.1136/jitc-2019-000453
53. Yi M, Jiao D, Xu H, Liu Q, Zhao W, Han X, et al. Biomarkers for Predicting Efficacy of PD-1/PD-L1 Inhibitors. *Mol Cancer* (2018) 17(1):129. doi: 10.1186/s12943-018-0864-3
54. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. *New Engl J Med* (2017) 377(25):2500–1. doi: 10.1056/NEJMc1713444
55. Zhao P, Li L, Jiang X, Li Q. Mismatch Repair Deficiency/Microsatellite Instability-High as a Predictor for Anti-PD-1/PD-L1 Immunotherapy Efficacy. *J Hematol Oncol* (2019) 12(1):54. doi: 10.1186/s13045-019-0738-1
56. Jin Z, Sinicrope FA. Prognostic and Predictive Values of Mismatch Repair Deficiency in Non-Metastatic Colorectal Cancer. *Cancers* (2021) 13(2):300. doi: 10.3390/cancers13020300
57. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol Off J Am Soc Clin Oncol* (2020) 38(1):1–10. doi: 10.1200/jco.19.02105
58. Pelekanou V, Barlow WE, Nahleh ZA, Wasserman B, Lo YC, von Wahlde MK, et al. Tumor-Infiltrating Lymphocytes and PD-L1 Expression in Pre- and Posttreatment Breast Cancers in the SWOG S0800 Phase II Neoadjuvant Chemotherapy Trial. *Mol Cancer Ther* (2018) 17(6):1324–31. doi: 10.1158/1535-7163.MCT-17-1005
59. Cao L, Huang C, Cui Zhou D, Hu Y, Lih TM, Savage SR, et al. Proteogenomic Characterization of Pancreatic Ductal Adenocarcinoma. *Cell* (2021) 184 (19):5031–52 e26. doi: 10.1016/j.cell.2021.08.023
60. Antonarakis ES, Isaacsson Velho P, Fu W, Wang H, Agarwal N, Sacristan Santos V, et al. CDK12-Altered Prostate Cancer: Clinical Features and Therapeutic Outcomes to Standard Systemic Therapies, Poly (ADP-Ribose) Polymerase Inhibitors, and PD-1 Inhibitors. *JCO Precis Oncol* (2020) 4:370–81. doi: 10.1200/po.19.00399

61. Wang F, Zhao Q, Wang YN, Jin Y, He MM, Liu ZX, et al. Evaluation of POLE and POLD1 Mutations as Biomarkers for Immunotherapy Outcomes Across Multiple Cancer Types. *JAMA Oncol* (2019) 5(10):1504–6. doi: 10.1001/jamaoncol.2019.2963

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frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 14 July 2022
doi: 10.3389/fonc.2022.891886

Phase II Study of ENZAlutamide Combined With Hypofractionated Radiation Therapy (ENZART) for Localized Intermediate Risk Prostate Cancer

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OPEN ACCESS

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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: *08 March 2022*
Accepted: *01 June 2022*
Published: *14 July 2022*

Citation:
Lara PC, Rodríguez-Melcón JI, Palacios-Eito A, Lozano A, Hervás-Morón A, Villafranca E, Gómez-Iturriaga A, Sancho G and Maldonado X (2022) Phase II Study of ENZAlutamide Combined With Hypofractionated Radiation Therapy (ENZART) for Localized Intermediate Risk Prostate Cancer. Front. Oncol. 12:891886. doi: 10.3389/fonc.2022.891886

Background: Intermediate-risk prostate cancer (PCa) is usually treated by a combination of external beam radiation therapy (EBRT) and a short course of androgen deprivation therapy (ADT). ADT is associated with multiple side effects, including weight gain, loss of libido, and hot flashes. In contrast, anti-androgen monotherapy is generally better tolerated in spite of higher rates of gynecomastia.

Objective: This study assessed the effectiveness of enzalutamide monotherapy combined with hypofractionated EBRT (Hypo-EBRT) for treating intermediate risk prostate cancer.

Method: This trial was a multicenter, open-label phase II study of 6 months of enzalutamide monotherapy combined with Hypo-EBRT for intermediate-risk prostate cancer. Hypo-EBRT was initiated 8–12 weeks after initiating enzalutamide. The primary endpoint was PSA decline >80% measured at the 25th week of enzalutamide administration. Secondary end-points included assessment of toxicity, changes in anthropomorphic body measurements, sexual hormones, and metabolic changes.

Results: Sixty-two patients were included in the study from January 2018 to February 2020. A PSA decline of >80% was observed in all evaluable patients at the end of enzalutamide treatment and 92% achieved PSA values under 0.1 ngr/ml. All patients remain in PSA response (<80% reduction of the initial values) 6 months after the end of

enzalutamide treatment. The most frequent adverse events were hypertension, asthenia, and gynecomastia. There were no significant changes in bone density, body mass index (BMI), or patient-reported outcomes (PROs).

Conclusion: Enzalutamide monotherapy is very effective along with hEBRT in reducing PSA levels for patients with intermediate-risk prostate cancer. Longer follow-up is needed to confirm the potential use of this combination in future randomized trials.

Keywords: prostate cancer, intermediate risk, enzalutamide monotherapy, hypofractionated, radiotherapy

INTRODUCTION

Radiation therapy (RT) is the standard treatment for localized prostate cancer patients (1). When external beam radiotherapy (EBRT) is used, conventionally fractionated external beam RT (cEBRT) with total escalated doses of 75.6–79.2 Gy (2) is usually prescribed.

Due to the favorable α/β ratio of prostatic cancer, as compared to the surrounding normal tissues (3), the use of hypofractionated schedules would be of interest. For patients, hypofractionated EBRT (Hypo-EBRT) is very convenient, as it reduces the treatment time, improves access to treatment, and lowers the treatment cost (4). Hypo-EBRT administered in 4 to 5 weeks had resulted, in an equivalent disease control rate, compared with escalated cEBRT administered at 8 weeks, with similar acute and late toxicity rates in non-inferiority randomized trials (5–7).

Androgen deprivation therapy is usually combined as adjuvant treatment with EBRT in localized and locally advanced prostate cancers (8). Although it is effective in reducing tumor mass and prostate-specific antigen (PSA) levels (9), limitations to the use of adjuvant ADT in these localized tumors mainly derive from the short- and long-term adverse effects (AEs), which may worsen the quality of life of the patient or be potentially harmful (10–12).

Antiandrogens are considered an alternative to ADT along with EBRT. The use in monotherapy of the first-generation antiandrogen, bicalutamide, along with cEBRT, improves survival in prostate cancer patients in very unfavorable situations without resulting in testosterone-suppression-induced side effects (13–15).

Enzalutamide is a second-generation oral androgen receptor (AR) inhibitor (16) that, unlike classical antiandrogens, blocks different steps in the AR signaling pathway (17, 18). In castration resistant metastatic patients, enzalutamide resulted in better clinical outcomes and reduced toxicity when compared with bicalutamide and ADT (19). Enzalutamide plus ADT is approved for treating adult men with castration-sensitive or resistant metastatic prostate cancer (20–23).

The possibility of using enzalutamide as monotherapy has been extensively studied by Tombal et al. (24–26) as the first treatment in patients with localized and metastatic prostate cancer. They chose the PSA response (<80% PSA decline over pretreatment levels) to assess the activity of enzalutamide, according to previous results from prospective studies with the LHRH antagonist degarelix (27). The use of enzalutamide has a better tolerance profile than LH-RH agonists in terms of body mass, lipid profile, or bone density. The quality of life of the patients did not change with the treatment, and from the sexual perspective, the results were similar to those of bicalutamide. As testosterone levels remain elevated during enzalutamide treatment, sexual toxicity is lower than that observed with ADT therapy, but there was a higher rate of disorders related to the breast (24–26).

Therefore, enzalutamide in monotherapy in men with previously untreated prostate cancer produces an adequate level of suppression of the disease as measured by a long and sustained decrease in PSA with less toxicity than LH-RH agonists (26).

Then, if localized intermediate-risk prostate cancer is to be managed with a combination of radiotherapy and hormonal therapy (28), the possibility of improving the toxicity profile of this treatment, using enzalutamide monotherapy, would be of great benefit to these patients with a good prognosis, who should not suffer bothersome undesirable effects.

Enzalutamide monotherapy radiosensitizes prostate cancer cells to radiation (29) by inducing the suppression of DNA repair mechanisms, mainly through non-homologous end-joining repair suppression mediated by DNAPKc proteins (30). This sensitizing effect was also demonstrated in androgen-sensitive and resistant prostate cancer cell lines, animal models, and xenografts on castration-resistant human prostate cancers (31). Enzalutamide provides a stronger radiosensitation than ADT (32) and, furthermore, this effect is more relevant when higher than 2 Gy doses per fraction (29) are used and enzalutamide is administered concurrently with RT (31). This improved effect on concomitant-adjuvant hormonal therapy with radiotherapy has also been observed for standard ADT in the clinical setting (33).

Therefore, if we consider the use of enzalutamide along with radiotherapy for localized prostate cancer, several questions still need to be answered. First, the immediate acute tumor response estimated by PSA decline of combined enzalutamide with the new standard modern Hypo-EBRT. This Hypo-EBRT schedule would favor radiosensitization induced by enzalutamide and improve tumor response. Second, there is no evidence about the possibility of a durable PSA response after cessation of enzalutamide treatment. This issue is of particular interest as it would encourage the development of future trials comparing standard ADT with enzalutamide monotherapy in this particular setting. Third, the toxicity of such a combination and the quality of life of prostate cancer patients are still unknown.

Based on the clinical and biological findings, we analyze for the first time the use of modern hEBRT along with concurrent enzalutamide monotherapy as treatment for localized intermediate-risk prostate cancer.

PATIENTS AND METHODS

This open-label, single-arm, phase 2 study was done across 8 recruiting sites in Spain. Patients were enrolled if they were aged 18 years or older; had histologically confirmed localized **(after diagnostic work-up, namely, pelvic MRI and/or abdomen CT-scan and bone-scan)** intermediate risk prostatic adenocarcinoma (defined as PSA 10–20 ng/ml and/or T2b-C and/or Gleason score 7, if all three factors were present, less than 50% of cores were required to be positive); had an Eastern Cooperative Oncology Group (ECOG) score of 0–1, adequate renal/liver function, and normal blood counts.

Exclusion criteria included previous or current hormonal manipulation, prior treatment for prostate cancer, previous radiation therapy for a pelvic tumor, history of cancer in the last 5 years, history of seizure or treatment with antiepileptic drugs. The full inclusion/exclusion criteria are given in **Supplementary Material Table 1**.

All patients provided written informed consent. This study was conducted in accordance with the Helsinki Declaration and the International Conference on Harmonization: Harmonized Tripartite Guideline: Guideline for Good Clinical Practice. The protocol was approved by local institutional review boards of each center, independent ethics committees, and the Anonymized for Review Government Competent Authority in Spain. The trial was registered at ClinicalTrials.gov, NCT01302041.

Procedures

After a 4-week screening period, the participants were given a study drug-dosing diary for each of the 6 treatment cycles. Each treatment cycle lasted 28 days (4 weeks), while the participant received the study drug enzalutamide orally. Starting on Day 1, all patients will ingest enzalutamide 160 mg/day at the same time each day, without breaks (except as outlined for toxicity), for 6 (28 days ±3 days) cycles. The dose reduction of enzalutamide to 120 mg/day was allowed with the approval of the principal investigator of the study. Patients were instructed to return all unused capsules at each study visit to assess compliance and received the study drug every 28 days (± 3 days) for 6 cycles.

In patients suffering from grade 3 or greater toxic side effects that cannot be reduced by the use of standard medical intervention, treatment should be interrupted until these adverse effects improve. Then, patients could restart on a reduced enzalutamide dose with the written approval of the principal investigator of the study.

Between 8 and 12 weeks after starting enzalutamide, the patients were treated with Hypo-EBRT for a duration of 5.5 weeks. Treatment was administered on an outpatient basis. Hypo-EBRT was administered under Image Guided Radiation Therapy (IGRT) technology. The participant centers were required to routinely use IGRT in these patients, either by ConeBeam CT study and/or fiducial markers placed within the prostate. The External Beam Radiation Dose was normalized such that exactly 98% of the PTV (planned target volume) receives the prescription dose and will be scored as per protocol. The maximum allowable dose within the PTV is 107% of the prescribed dose to a volume that is at least 0.03 cc. The minimum allowable dose within the PTV is >95% of the prescribed dose to a volume that is at least 0.03 cc. The EBRT/IGRT protocol delivered a total dose to the PTV (CTV including the prostate and the proximal seminal vesicles with a 4 mm posterior margin, 8 mm lateral margin, and 5 mm margin in all other directions) of 70 Gy delivered in 28 fractions of 2.5 Gy each. The EQD2 (considering the alpha/beta ratio of 1.5 Gy) was 80 Gy (34).

Blood samples to establish PSA and circulating hormone levels were collected at screening, at the 4th and 25th weeks, and 1, 3, and 6 months after the end of enzalutamide. All patients had monthly clinical visits during treatment and safety follow-up visits at 1, 3, and 6 months after their last dose of enzalutamide, recording adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Blood samples assessing renal, liver, and blood counts were performed at screening and monthly until the end of enzalutamide administration. Fasting serum lipids and fasting glucose levels were assessed on samples collected on day 1, the 12th, and the 25th weeks.

Changes in bone mineral density were assessed by a dual-energy X-ray absorptiometry scan on day 1 and the 25th week. HRQoL was assessed with self- administered EORTC QLQ-C30 and EORTC QLQ-PR25 instruments (35, 36) completed by patients on day 1, at the 12th and 25th week, and at the safety follow-up visit 1 month after the end of enzalutamide.

Outcomes

The primary outcome was PSA response, defined as a decline from baseline in PSA level of 80% or greater at the 25th week, based on the PSA response observed in registration trials of enzalutamide and other hormonal treatments (24, 27). Enzalutamide-induced PSA decline after 1, 3, and 6 months of cessation of enzalutamide treatment for the primary analysis has also been considered a relevant treatment response marker to assess the activity of enzalutamide combined with hypofractionated radiotherapy. Secondary outcomes were, changes from baseline in hormone level, bone mineral density, fasting serum lipids and quality of life. Safety outcomes included the frequency and severity of adverse events as scored by the CTCAE 4.0.

Statistical Analysis

The primary activity outcome was the proportion of patients with a PSA response at the 25th since the start of enzalutamide and 1, 3, and 6 months after the cessation of enzalutamide treatment. This was calculated as the number of patients with PSA response (≥80% PSA decline from baseline) at the prespecified time-points, divided by the number of patients who started treatment, and presented as the percentage of patients responding. Patients who discontinued enzalutamide treatment were included in the intention-to-treat analysis. Secondary and exploratory outcomes are summarized descriptively.

The primary endpoint for this trial was to assess the number of patients with a more or equal 80% reduction in baseline PSA at the 25th week. We assume a null hypothesis if 70% of patients do not achieve PSA declines of over 80% and a positive hypothesis if more than 85% of the patients achieve such a decline at the 25th week. We aimed for a "maximum" recruiting scenerio, calculating the target evaluable sample size for an alpha = 0.05 and beta = 0.1 error to be 66 patients, resulting in 70 cases of target recruiting size if a 5% patient loss was considered. A second "standard" calculation of the target evaluable sample size for an alpha = 0,05 and beta = 0.2 error, resulted in 47 evaluable patients to be recruited, reaching 50 patients if a 5% loss was considered.

Safety analyses were performed on all patients who had taken at least one dose of the study drug. All reported toxicities were summarized as acute toxicity regardless of attribution by maximum grade and were sorted by the number of patients experiencing the toxicity during the enzalutamide and Hypo-EBRT treatments and until 1 month post-treatment. Late toxicity was recorded at 6 months after cessation of enzalutamide.

Activity analysis was performed according to the "intention to treat" analysis, including patients who had taken at least one dose of study drug and had both pretreatment and at least one activity evaluation after treatment initiation.

The mean, standard deviation, range, and 95% confidence interval of the mean were calculated to describe the quantitative variables. The Shapiro–Wilk (n ≤50) or Kolmogorov–Smirnov (n >50) test was used to verify the normality of the data of the quantitative variables as a function of the sample size. The qualitative variables have been described by means of the absolute frequency, relative frequency, and the CI (95%) calculated using the Clopper–Pearson method. When the sample size is greater than 30, the Student's t-test has been used for paired data to compare numerical variables at two different moments of time. In the opposite case, and if the variables do not follow a normal distribution, we have used the Wilcoxon test for paired data. A p-value of less than 0.05 is considered significant. The statistical program used was R Core Team 2021, version 4.1.1 (37).

Role of the Funding Source

This is an independent academic study supported by an unrestricted educational grant from Astellas. The authors performed the protocol design, data analysis, interpretation, and preparation of this report. Data analysis was performed by an independent statistician (JMGM). All authors had access to the study data. All decisions relating to the manuscript writing and content were made jointly by the authors, including the final decision to submit it for publication.

RESULTS

Patient's Characteristics

Sixty-two out of the maximum recruiting scenery of 70 patients were finally included in the present study from 16 January 2018 to 4 February 2020. The study was closed earlier than expected to achieve the maximum recruiting schedule (31 March 31 2020), due to the COVID-19 pandemic that strongly affected Spain. The number of recruited patients at that time was already over the expectation of the standard calculated sample size, heading for an alpha = 0.05 and beta = 0.2 error.

Four patients resulted in screening failure, and one patient retracted consent after the screening period. Patients and tumor characteristics for the 57 patients who started enzalutamide treatment are described in **Table 1**. Most patients (32/57, 73.7%) were classified as unfavorable intermediate NCCN risk subgroups.

Protocol Compliance and Security

One of the 57 patients taking enzalutamide, retract consent to participate in the study at the 4th week due to general discomfort, unrelated to any objective toxicity. Therefore, 56 patients were finally included in the study (**Figure 1**).

During enzalutamide treatment, three severe adverse effects were reported. One severe hepatic toxicity (Grade 4) related to enzalutamide, displaying a rise in liver enzymes at the 7th week, normalized after complete and definitive enzalutamide cessation. The responsible investigator considered this adverse effect as related to enzalutamide. Anyhow, the patient continued with the study program evaluations and tests. Two patients suffered severe adverse effects non-related to enzalutamide. One patient had sepsis after fiducial implantation in the prostate for IGRT in the 2nd week, and one patient suffered an ictus in the 9th week. This patient had a previous hypertensive clinical history, and the event was not related by the responsible investigator to enzalutamide treatment. Both patients completed the enzalutamide treatment but with a dosage reduction to 120 mg/day as per protocol in the hypertensive patient.

One patient abandoned enzalutamide treatment at week 11 due to general discomfort unrelated to any objective toxicity. The patient agreed to continue the study follow-up. Two patients from the same center misunderstood the trial instructions and stopped enzalutamide during the 5 weeks of radiotherapy treatment.

Radiotherapy was administered as scheduled (total dose of 70 Gy in 28 fractions, 2.5 Gy per fraction) to all 56 patients. All 56 cases but one (a patient who started radiotherapy in the 5th week) started radiotherapy between the 8th and the 13th week as scheduled. Radiotherapy was completed in all cases, for a total treatment time of 41.63 ± 3.30 days (CI 95% 40.75–42.51). Dosimetry recommendations were well accomplished in all cases. IIn most cases, PTV coverage and OAR constraints were achieved in most cases (**Supplementary Material Table 2**).

Acute toxicity was recorded as the maximum toxicity observed during treatment and until one month after cessation of enzalutamide (**Table 2**). Two patients, as described above, presented grade 4 toxicity (hypertensive in one case, liver enzyme elevation in the other case). Severe grade 3 acute systemic toxicity observed was related to hypertension (systolic in all cases) in 19/56 (33.93%). Urinary and gastrointestinal toxicity 2 were present in 18/56 (32.14%) and 5/56 (8.9%) patients, respectively. Common (one third of the cases) mild toxicity included asthenia, breast pain, gynecomastia, urinary pain, and polaquiuria (**Table 3**). Other acute

TABLE 1 | Patient Characteristics (n = 57).

	N
Age (years)	71.7 (50–83)
T Stage	
T1c	35 (61.4%)
T2a	15 (26.3%)
T2b	3 (5.3%)
T2c	4 (7.0%)
N stage	
Nx	0 (0%)
N0	57 (100%)
N1	0 (0%)
M stage	
Mx	0 (0%)
M0	57 (100%)
M1	0 (0%)
Gleason Score	
6	3 (5.3%)
7	54 (94.7%)
3 + 4	29 (53.7%)
4 + 3	25 (46.3%)
Affected biopsy cores (%)	38.7 (8–100)
Pretreatment PSA ng/ml	
≤10	46 (80.70%)
>10	11 (19.30%)
NCCN risk subgroup	
Favorable	15 (26.3%)
Unfavorable	32 (73.7%)
ECOG	
0	56 (98.24%)
1	1 (1.76%)
Charlson score	
0–1	48 (84.21%)
2	5 (8.77%)
3	3 (5.30%)
Unknown	1(1.76%)
Body Mass Index	
<25	8 (14.03%)
25–30	31 (54.38%)
>30	12 (21.05%)
Unknown	6 (10.52%)
Basal Hypertension	
<140/90	19 (33.33%)
>141/91	31 (54.38%)
Unknown	7 (12.28%)
Basal elevated Cholesterol/Triglicerides	
No	23 (40.35%)
Yes	19 (33.33%)
Unknown	15 (26.32%)
Basal elevated ALT/AST	
Yes	3 (5.27%)
No	54 (94.73%)

general, hormonally-related and gastrointestinal toxicity were also mild and uncommon.

Late toxicity was recorded 6 months after enzalutamide cessation. Most of the urinary and hypertensive severe toxicity disappeared. Toxicity was mainly related to hormonally derived symptoms such as breast pain and gynecomastia. Severe grade 3 toxicity was present in 2 patients, one with urinary pain and retention, and the other showing grade 3 proctitis. Grade 3 hypertension was observed in 5 patients (**Table 2**).

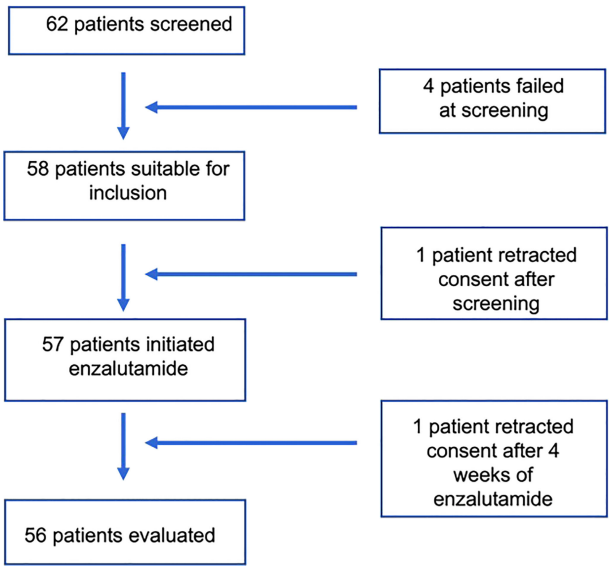

FIGURE 1 | Protocol Flow Chart.

PSA

All 56 patients included in the study were analyzed for PSA response in an intention-to-treat analysis and evaluated according to the PSA response data time-point available. All 56 patients evaluable for PSA treatment-induced modifications at pre-specified time points showed PSA reduction higher than 80%. At the 25th week, all evaluable patients (50 cases) achieved PSA values of 0.2 ng/ml and PSA was under detectable levels (<0.1 ng/ml) in 92% of all patients (**Table 3**). PSA values dropped from pretreatment levels of 7.61 ± 2.82 (3.53–16.77) ng/ml to 0.04 ± 0.04 (0.00–0.16) ng/ml at the 25th week and remained low 6 months after cessation of enzalutamide (**Table 4**).

Hormone Levels

Patients treated with enzalutamide showed a sharp increase in testosterone and estradiol after 4 weeks of enzalutamide treatment (**Table 4**). LH and FSH levels were also increased at week 25. Testosterone and estradiol levels decreased to pretreatment levels, but LH and FSH levels remained elevated at 6 months (**Figure 2**).

Anthropometric, bone, and metabolic changes at a pre-specified time point.

At the time of last evaluation, there was no statistically significant weight change after enzalutamide treatment, either in bone density as measured in densitometric analysis or the bone resorption marker, alkaline phosphatase. Metabolic changes in fasting glucose, cholesterol, or triglyceride levels were not present after enzalutamide treatment. There was a modest increase in HDL cholesterol at the last evaluation (**Table 5**).

TABLE 2 | Maximum grade acute and late adverse effect after treatment in 56 evaluable patients.

	Acute Toxicity			Late Toxicity		
	G1	G2	G3	G1	G2	G3
General Symptoms						
Hypertension	10 (17.86%)	26 (46.43%)	19 (33.93%)	18 (45.0%)	17 (42.50%)	5 (12.50%)
Asthenia	18 (32.14%)	3 (5.36%)		2 (3.57%)		
AST/ALT elevation	11 (19.64%)					
Somnolence/Insomnia	5 (8.93%)			3 (5.36%)		
Headache/loss of concentration	1 (1.79%)	1 (1.79%)		1 (1.79%)		
Dizzines/ortostasim	6 (10.71%)	1 (1.79%)	1 (1.79%)		1 (1.79%)	
Depression/Anxiety	1 (1.79%)	1 (1.79%)		3 (5.36%)		
Dry skin	3 (5.36%)	1 (1.79%)		2 (3.57%)		
Skin hyperpigmentation folliculitis	2 (3.57%)			1 (1.79%)		
Mialgia/leg discomfort	3 (5.36%)					
Arthralgia	3 (5.36%)			1 (1.79%)		
Symptoms related to hormonal changes						
Breast Pain	14 (25.00%)	3 (5.36%)		11 (19.64%)		
Nipple pain/discomfort	3 (5.36%)			1 (1.79%)		
Gynecomastia	13 (23.21%)	5 (8.93%)		8 (14.29%)		
Hot flashes	2 (3.57%)			1 (1.79%)		
Libido Decreased	7 (12.50%)			6 (10.71%)		
Retrograde ejaculation	2 (3.57%)			2 (3.57%)		
Hipogonadism	2 (3.57%)			1 (1.79%)		
Urinary symptoms						
Pain	12 (21.43%)	6 (10.71%)	1 (1.79%)			1 (1.79%)
Urgency	13 (23.21%)	6 (10.71%)	3 (5.36%)	1 (1.79%)		
Incontinence	9 (16.07%)			1 (1.79%)		
Polaquiuria	4 (7.14%)	8 (14.81)	2 (3.57%)			
Retention/obstruction	2 (3.57%)	4 (7.14%)	1 (1.79%)			1 (1.79%)
Non infectous cystitis	4 (7.14%)	1 (1.79%)				
Nicturia		1 (1.79%)				
Gastrointestinal Symptoms						
Abdominal Pain	4 (7.14%)			2 (3.57%)		
Rectal Pain	4 (7.14%)	1 (1.79%)		1 (1.79%)		
Proctitis	7 (12.50%)	2 (3.57%)				1 (1.79%)
Anorexia/Hyporexia	5 (8.93%)	1 (1.79%)		1 (1.79%)		
Disgeusia	2 (3.57%)	1 (1.79%)				
Constipation/Diarrhea	8 (14.29%)					
Nausea/Vomitting	5 (8.93%)	1 (1.79%)				
Meteorism	2 (3.57%)					

Acute grade 4 was observed in 2 patients (one hypertensive crisis and one elevation of AST/ALT). No grade 4 late toxicity was observed.

Patients Reported Outcomes (PROs) at Pre-Specified Time Points

PROs were analyzed through the EORTC QLQC30 and EORTC QLQ-PR25 at pretreatment, the 12th week of treatment, at the 25th week, and one month after cessation of enzalutamide. A reduction in QoL scores as estimated by the EORTC QLQC30 and an increase in symptoms were observed at the 12th and 25th weeks, recovering one month after cessation of the treatment. Specific PRO analysis of symptoms related to prostate cancer treatment (EORTC-QLQ-PR25) showed a significant impact on the urinary domain during the radiotherapy treatment period (12th–25th week) that recovered one month after cessation of

TABLE 3 | PSA decline values at pre-specified time points.

	25th week (n = 50)	1 month after enzalutamide (n = 51)	3 months after enzalutamide (n = 51)	6 months after enzalutamide (n = 51)
PSA decline ≥80%	50/50 (100%) (95% CI: 92.89–100%)	51/51 (100%) (95% CI: 93.02–100%)	51/51 (100%) (95% CI: 93.02–100%)	51/51 (100%) (95% CI: 93.02–100)
PSA decline ≥90%	50/50 (100%) (95% CI: 92.89–100%)	51/51 (100%) (95% CI: 93.02–100%)	46/51 (90.2%) (95% CI: 78.59–96.74%)	45/51 (88,24%) (95% CI: 76.13–95.56%)
PSA <0.2 ng/ml	50/50 (100%) (95% CI: 92.89–100%)	42/51 (82.3%) (95% CI: 69.13–91.6%)	29/51 (56.8%) (95% CI: 42.25–70.65%)	26/51 (50.98%) (95% CI: 36.6–65.25%)
PSA <0.1 ng/ml	44/50 (88%) (95% CI: 75.69–95.47%)	37/51 (72.5%) (95% CI: 58.26–84.11%)	13/51 (25.5%) (95% CI: 14.33–39.63)	9/51 (17.6%) (95% CI: 8.4–30.87%)

TABLE 4 | PSA and hormone profile values at pre-specified time points.

	Pretreatment	4th week	25th week	1 monthafter enza	3 months after enza	6 months after enza	P-value
PSA (ng/ml)	(n = 56)	(n = 52)	(n = 50)	(n = 51)	(n = 51)	(n = 51)	Pre vs 4th w: p <0.0001 Pre vs 25th w p <0.0001
Mean ± SD	7.61 ± 2.82	2.98 ± 2.37	0.04 ± 0.04	0.09 ± 0.12	0.28 ± 0.29	0.29 ± 0.28	Pre vs 1 m p <0.0001
(range)	(3.53–16.77)	(0.22–11.50)	(0.00–0.16)	(0.00–0.52)	(0.01–1.21)	(0.01–1.11)	Pre vs 3 m p <0.0001
95% CI	6.87–8.35	2.33–3.62	0.03–0.05	0.06–0.12	0.20–0.36	0.21–0.36	Pre vs 6 m p <0.0001
Testosterone (ng/ml)	(n = 53)	(n = 48)	(n = 48)	(n = 48)	(n = 49)	(n = 46)	Pre vs 4th w: p <0.0001 Pre vs 25th w p <0.0001
Mean ± SD	5.41 ± 2.74	9.83 ± 4.18	9.16 ± 4.52	8.04 ± 4.25	7.49 ± 10.55	4.82 ± 3.633	Pre vs 1 m p <0.0001
(range)	(2.20–18.19)	(3.11–19.00)	(1.70–21.10)	(1.40–24.27)	(1.70–69.35)	(1.30–25.91)	Pre vs 3 m p = 0.154
95% CI	4.68–6.15	8.65–11.02	7.88–10.44	6.84–9.25	4.53–10.44	3.77–5.87	Pre vs 6 m p = 0.285
Estradiol (pg/ml)	(n = 48)	(n = 44)	(n = 45)	(n = 44)	(n = 41)	(n = 39)	Pre vs 4th w: p <0.0001 Pre vs 25th w p <0.0001
Mean ± SD	26.52 ± 9.59	44.40 ± 17.56	41.72 ± 19.93	40.37 ± 16.78	30.05 ± 10.61	30.59 ± 10.62	Pre vs 1 m p <0.0001
(range)	(10.00–47.70)	(14.00–87.00)	(0.00–85.00)	(0.00–72.00)	(12.00–51.00)	(10.00–54.00)	Pre vs 3 m p = 0.015
95% CI	23.80–29.23	39.21–49.59	35.90–47.54	35.41–45.33	26.80–33.30	27.25–33.92	Pre vs 6 m p = 0.057
LH (mUI/ml)	(n = 51)	(n = 49)	(n = 49)	(n = 46)	(n = 44)	(n = 45)	Pre vs 4th w: p <0.0001 Pre vs 25th w p <0.0001
Mean ± SD	6.99 ± 4.98	13.19 ± 6.69	19.24 ± 8.46	17.49 ± 8.47	12.56 ± 6.67	11.12 ± 5.43	Pre vs 1 m p <0.0001
(range)	(2.08–30.72)	(4.83–35.95)	(7.34–39.20)	(7.24–39.40)	(5.50–32.60)	(4.68–30.24)	Pre vs 3m p <0.0001
95% CI	5.62–8.36	11.32–15.07	16.87–21.61	15.04–19.94	10.59–14.53	9.54–12.71	Pre vs 6m p <0.0001
FSH (mUI/ml)	(n = 48)	(n = 45)	(n = 44)	(n = 41)	(n = 40)	(n = 40)	Pre vs 4th w: p = 0.055 Pre vs 25th w p <0.0001
Mean ± SD	13.73 ± 18.77	15.11 ± 18.68	28.86 ± 15.51	27.14 ± 13.95	27.49 ± 12.08	27.43 ± 12.70	Pre vs 1 m p <0.0001
(range)	(2.20–126.24)	(2.30–116.44)	(9.20–81.17	(11.40–88.66)	(10.68–79.05)	(9.51–84.71)	Pre vs 3m p <0.0001
95% CI	8.42–19.04	9.66–20.57	24.27–33.44	22.87–31.41	23.74–31.23	23.49–31.36	Pre vs 6m p <0.0001

treatment. Gastrointestinal and sexual domains did not change significantly during treatment and completely recovered at the end of the study period. Changes in the hormonal domain remained significantly present one month after enzalutamide treatment (**Table 6**, **Figure 3**).

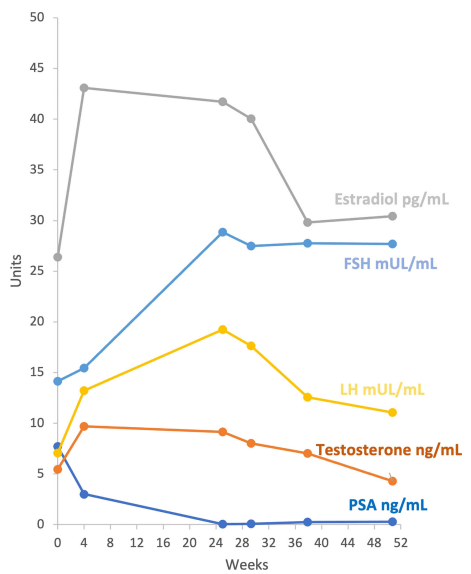

FIGURE 2 | Graphical presentation of PSA and Hormonal profile at pre-specified timepoints. Data in Y-axis represent number of units (type of units for each parameter is displayed in the figure lines). Data in X- axis represent number of weeks after pretreatment assessment.

DISCUSSION

Patients having localized intermediate prostate cancer are usually treated with a combination of radiation therapy and 6 months of ADT. Previous studies have shown an excellent toxicity profile of enzalutamide monotherapy compared with ADT (26). Furthermore, combined enzalutamide and conventionally fractionated radiotherapy has been shown to be well tolerated in this particular clinical situation (38). But little is known about the toxicity and PROs when enzalutamide monotherapy is discontinued.

Our study was planned to assess the role of enzalutamide monotherapy combined with modern hypofractionated EBRT for treating patients with localized intermediate-risk prostate cancer.

As previously described in other studies (24), our patients showed a better toxicity profile than that traditionally described in ADT trials, caused by the compensatory elevation of sexual hormones. No changes in body mass index, bone density mass, fasting glucose, cholesterol, or libido were found one month after the end of enzalutamide. Just after the end of enzalutamide treatment, modest changes in HDL-cholesterol were still evident.

As expected, testosterone, estradiol, LH, and FSH levels sharply increase during enzalutamide treatment (24). Our data showed for the first time that testosterone and estradiol levels tend to return to basal levels 6 months after cessation of enzalutamide, although LH and FSH remain elevated.

This fact, would be relevant when assessing the acute and long-term hormonal side effects analyzed either by the physicians, through the CTCAE4.0 toxicity scale [Physician Reported Outcomes, (PhyROs)] or the patients, through the EORTC QLQC30 and EORTC QLQ-PR25 (PROs). In fact, no

TABLE 5 | Antropometric, bone and metabolic changes at pre-specified time point.

	Pretreatment	12th week	25th week	1 month after enza	P-value
Body Mass Index	(n = 50)	(n = 46)	(n = 40)	(n = 40)	
Mean ± SD	28.30 ± 4.55	27.55 ± 4.83	27.30 ± 4.18	27.38 ± 4.11	Pre vs 12th w: p <0.0001
(range)	(17.03–44.39)	(16.78–44.46)	(17.32–40.04)	(20.57–40.57)	Pre vs 25thw: p = 0.001
95% CI	27.04–29.56	26.16–28.95	26.01–28.60	26.11–28.66	Pre vs 1 m: p = 0.082
Bone Density Femoral Neck (g/cm^2)	(n = 45)		(n = 45)		
Mean ± SD	0.85 ± 0.15		0.86 ± 0.15		Pre vs 25th w: p = 0.253
(range)	(0.58–1.35)		(0.61–1.25)		
95% CI	0.80–0.89		0.82–0.91		
Bone Density Lumbar Spine (g/cm^2)	(n = 48)		(n = 48)		
Mean ± SD	1.13 ± 0.21		1.14 ± 0.21		Pre vs 25th w: p = 0.342
(range)	(0.77–1.87)		(0.77–1.92)		
95% CI	1.07–1.19		1.08–1.20		
Alkaline Phosphatase (U/L)	(n = 49)	(n = 44)	(n = 49)		
Mean ± SD	72.61 ± 27.65	65.48 ± 17.63	76.59 ± 25.78		Pre vs 12thw: p = 0.033 Pre vs 25thw: p = 0.093
(range)	(39.00–226.00)	(38.00–139.00)	(36.00–186.00)		
95% CI	64.87–80.36	60.27–70.69	69.37–83.81		
Fasting Glucose (mg/dl)	(n = 54)	(n = 46)	(n = 50)	(n = 50)	
Mean ± SD	113.67 ± 31.71	113.43 ± 28.76	115.68 ± 31.95	117.94 ± 32.22	Pre vs 12thw: p = 0.881
(range)	(83.00–253.00)	(70.00–253.00)	(83.00–247.00)	(80.00–263.00)	Pre vs 25thw: p = 0.886
95% CI	105.21–122.12	105.12–121.75	106.82–124.53	108.01–125.87	Pre vs 1 m: p = 0.758
Fasting Cholesterol Total (mg/dl)	(n = 38)	(n = 24)	(n = 37)		
Mean ± SD	185.58 ± 40.56	189.88 ± 34.69	198.44 ± 38.42		Pre vs 12thw: p = 0.218
(range)	(114.00–277.00)	(117.00–254.00)	(102.00–269.00)		Pre vs 25thw: p = 0.054
95% CI	172.69–198.48	176.00–203.75	186.06–210.82		
Fasting Cholesterol HDL (mg/dl)	(n = 33)	(n = 21)	(n = 32)		
Mean ± SD	54.19 ± 22.46	49.72 ± 10.30	58.37 ± 22.12		Pre vs 12thw: p = 0.382
(range)	(34.00–162.00)	(34.00–69.00)	(41.00–162.00)		Pre vs 25thw: p = 0.015
95% CI	46.52–61.85	45.31–54.12	50.71–66.03		
Fasting Cholesterol LDL (mg/dl)	(n=33)	(n = 20)	(n = 32)		
Mean ± SD	109.34±40.64	108.08 ± 30,33	116.37 ± 30.64		Pre vs 12thw: p = 0.409
(range)	(16.00-197.00)	(57.00–173.00)	(70.00–174.00)		Pre vs 25thw: p = 0.220
95% CI	95.47-123.20	94.79–121.37	105.75–126.98		
Fasting Triglicerides (mg/dl)	(n = 38)	(n = 20)	(n = 38)		
Mean ± SD	130.22 ± 55.97	142.78 ± 61.16	136.85 ± 56.90		Pre vs 12thw: p = 0.971
(range)	(54.00–265.00)	(54.00–313.00)	(56.00–301.00)		Pre vs 25thw: p = 0.165
95% CI	112.42–148.02	119.71–165.85	118.49–154.68		

sexual toxicity was observed, but gynecomastia (CTCAE 4.0) and hormonal related symptoms (QLQPR25) remained a problem for patients one month after the end of enzalutamide treatment.

In contrast, the global health status, the functioning area, or symptoms other than hormonally related, returned to pretreatment levels one month after cessation of enzalutamide.

The use of Hypo-EBRT is also a novelty in our study. We treated our patients according to the Hypo-EBRT protocol described by Kupelian et al. (34) and as the treatment arm in the RTOG 0415 trial (6). This schedule and others (39) provide the highest EQD2 (80 Gy) to the PTV, compared to other hypofractionated schemes (5–7). Our acute GU toxicity was slightly higher than that observed in the hypofractionated arm of the RTOG 0415 (32.9% vs 27%), while GI toxicity was very similar (8.9% vs 10.7%). Our 80 Gy EQD2 PTV included the proximal seminal vesicles (the first 1 cm of the seminal vesicles). This extra volume was not treated in the RTOG trial, as only low-risk patients were included in that trial. This higher PTV volume would be related to the slightly increased urinary toxicity found in our study (6). In the RTOG 0415 study, the hypofractionated arm had a very similar toxicity profile to the conventional arm. This conventionally fractionated radiotherapy scheme had a lower EQD2 (70 Gy) (6).

The study from Kaplan et al. (38) already analyzed this possibility by combining standard escalated cEBRT with enzalutamide monotherapy in intermediate-risk prostate cancer patients. Patients received conventionally fractionated EBRT to a total dose of 79.2 Gy at 1.8 Gy per fraction for 44 fractions (9 weeks), and enzalutamide was administered for 6 months. They reported only 6 cases out of 45 (13.33%) of ≧grade 2 urinary frequency. We observed this particular toxicity in 9/56 patients (16.06%). No data are available regarding the other GU toxicity items described in our study. We must note that due to the selected radiotherapy treatment in the Kaplan study (38) (1.8 Gy per fraction, 44 fractions to a total dose of 79.2), the EQD2 of this cEBRT is 74.67 Gy. This equivalent dose is well below the 80 Gy administered in our study.

The PROs recognized a temporary increase in urinary scores in the evaluations performed in the 12th week (just after the end of Hypo-EBRT) that was rapidly recovered at the end of the study period. However, no gastrointestinal or sexual symptom scores were changed.

TABLE 6 | Quality of Life assessment at pre-specified time points.

QLQ30	Pretreatment (n = 53)	12 th week (n = 50)	25th week (n = 47)	1 month after enzalutamide (n = 45)	P-value
Global Health					
Mean ± SD	82.55 ± 16.69	74.50 ± 19.30	80.50 ± 15.57	81.48 ± 18.02	Pre vs 12th w: p = 0.011
(range)	(33.33–100.00)	(16.67–100.00)	(50.00–100.00)	(33.33–100.00)	Pre vs 25th w: p = 0.155
95% **CI**	78.05–87.04	69.15–79.85	76.05–84.95	76.22–86.75	Pre vs 1 month: p = 0.682
Functioning area					
Mean ± SD	94.12 ± 7.19	88.53 ± 14.00	92.17 ± 8.53	92.05 ± 10.66	Pre vs 12th w: p = 0.011
(range)	(62.22–100.00)	(31.11–100.00)	(71.11–100.00)	(57.78–100.00)	Pre vs 25th w: p = 0.075
95% **CI**	92.18–96.05	84.65–92.41	89.73–94.61	88.97–95.13	Pre vs 1 month: p = 0.260
Symptoms Area					
Mean ± SD	2.95 ± 3.17	6.49 ± 6.45	4.71 ± 4.37	4.37 ± 4.75	Pre vs 12th w: p <0.001
(range)	(0.00–11.54)	(0.00–26.92)	(0.00–20.51)	(0.00–16.67)	Pre vs 25th w: p = 0.005
95% **CI**	2.10–3.80	4.70–8.28	3.46–5.96	3.00–5.75	Pre vs 1 month: p = 0.088
QLQ-PR25	**Pretreatment (n = 53)**	**12th week (n = 50)**	**25th week (n = 47)**	**1 month after enzalutamide (n = 47)**	**P-value**
Urinary Symptoms					
Mean ± SD	84.04 ± 12.60	69.51 ± 21.86	79.61 ± 17.64	81.84 ± 19.57	Pre vs 12th w: p <0.0001
(range)	(37.50–100.00)	(0.00–100.00)	(25.00–100.00)	(16.67–100.00)	Pre vs 25th w: p = 0.031
95% **CI**	80.65–87.43	63.45–75.57	75.57–84.65	76.39–87.29	Pre vs 1 month: p = 0.470
Gastrointestinal Symptoms					
Mean ± SD	97.01 ± 5.91	94.33 ± 9.44	96.45 ± 6.89	96.92 ± 5.92	Pre vs 12th w: p = 0.059
(range)	(75.00–100.00)	(50.00–100.00)	(75.00–100.00)	(75.00–100.00)	Pre vs 25th w: p = 0.569
95% **CI**	95.42–98.60	91.72–96.95	94.48–98.43	95.21–98.63	Pre vs 1 month: p = 0.844
Hormonal related symptoms					
Mean ± SD	96.54 ± 5.99	87.22 ± 10.86	84.75 ± 12.40	85.93 ± 10.42	Pre vs 12th w: p <0.0001
(range)	(72.22–100.00)	(50.00–100.00)	(55.56–100.00)	(55.56–100.00)	Pre vs 25th w: p <0.0001
95% **CI**	94.93–98.15	84.21–90.23	81.18–88.33	82.96–88.91	Pre vs 1 month: p <0.0001
Sexual activity					
Mean ± SD	77.04 ± 19.97	80.79 ± 25.00	72.86 ± 25.84	78.70 ± 25.84	Pre vs 12th w: p = 0.550
(range)	(33.33–100.00)	(5.56–100.00)	(11.11–100.00)	(16.67–100.00)	Pre vs 25th w: p = 0.232
95% **CI**	71.67–82.42	73.71–87.86	65.47–80.25	71.86–85.54	Pre vs 1 month: p = 0.822

The primary endpoint of the study deals with the efficacy of the combination of enzalutamide monotherapy and modern Hypo-EBRT, in terms of reduction of PSA levels, in patients with localized intermediate-risk prostate cancer, as used in similar trials (24–26, 38).

As stated earlier, activity analysis was performed with the intention of treating conditions. The PSA response was analyzed by the proportion of patients who showed a reduction of at least 80% of the initial values at the end of the 25 weeks of enzalutamide treatment. The seminal study by Tombal et al. (24) showed a PSA response of 92.5% (95% CI 86.2–98.8), similar to the 100% observed in our study. We also analyzed the kinetics of PSA reduction at pre-specified time-points (1, 3, and 6 months) after the cessation of enzalutamide. Our study showed that all patients remain in PSA response 6 months after the cessation of enzalutamide. Furthermore, 90% of the patients still showed a PSA decline of 90% of the pretreatment values, 6 months after the enzalutamide cessation. Obviously, the effect of radiotherapy on this maintained PSA decline is to be taken into account.

The study by Kaplan et al. (38) combined conventionally fractionated radiotherapy with enzalutamide monotherapy in intermediate-risk prostate cancer. They defined PSA response as PSA levels lower than 0.2 ng/ml at the end of 25 weeks of enzalutamide (39). Forty-nine out of 62 (79%) of their patients showed PSA response, in compared with 51/51 (100%) in our series for the same response evaluator. No data on PSA response was given after enzalutamide cessation in the Kaplan study, but 56.8% of our patients remained in the PSA response (<0.2 ng/ml) 6 months after enzalutamide cessation. Again, the lower EQD2 radiation dose in this study (74.67 Gy) the the present one (80 Gy) would explain the lower response rate observed.

The effect of radiotherapy along with enzalutamide versus enzalutamide alone, would only be indirectly analyzed by comparing the results from Tombal et al. (24) with those results from Kaplan and this study. Enzalutamide alone provided a 45% rate of undetectable PSA (<0.1 ng/ml) compared with 61.3% (38/62) for cEBRT and 88% for Hypo-EBRT. Although patient and tumor characteristics are of poorer prognosis in the enzalutamide alone trial (24), these data would shed light on the effect of radiotherapy along with enzalutamide in this particular setting.

Although available results regarding the role of enzalutamide and hypofractionated radiotherapy (38 and present series) are limited by the short follow-up, recent evidence seems to confirm the role of this approach in prostate cancer patients. Long-term evidence for the role of antiandrogen monotherapy as an alternative to ADT combined with hypofractionated radiotherapy comes from the CHiiP trial (40). In a *post hoc* analysis, they compared the results of 2,700 patients who

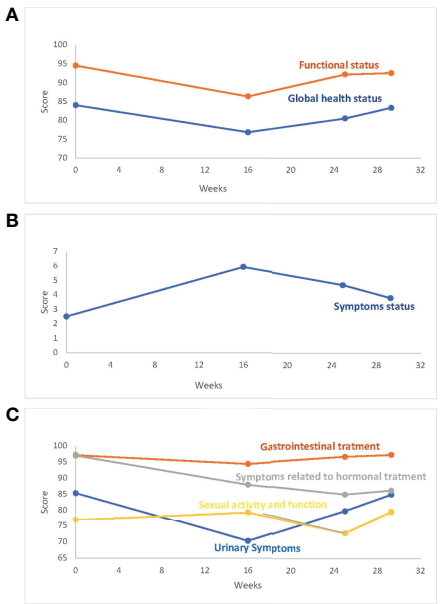

FIGURE 3 | PRO **(A)**. QLQ30_Global Health Status/Functional Status. **(B)** QLQ30_Symptoms Status. **(C)** QLQ_PR25. PROs score is displayed in the Y-axis. Weeks after pretreatment assessment are displayed in the X-axis.

received LHRHa and those of 403 patients who received bicalutamide (150 mg/day) as concomitant hormonal treatment. All characteristics of patient and tumor were similar among the two groups unless bicalutamide patients were significantly younger (median 67 vs 69 years LHRHa). After a median follow-up of 9.3 years, there was no difference in biochemical or clinical failure. Late toxicity, as estimated by the LENT-SOMA, was more frequently reported in LHRHa patients compared to bicalutamide patients. The quality of life was similar in both arms.

These mature results of a first-generation antiandrogen (bicalutamide) in monotherapy combined with hypofractionated radiotherapy would probably be confirmed when using a more active second-generation antiandrogen like enzalutamide in a similar setting.

The improvement in PSA response by adding radiotherapy to enzalutamide and the better response observed when using modern hypofractionated EBRT are related, in our opinion, not only to the higher EQD2 administered but to the biological basis of the radiosensitizing effect of enzalutamide. If protracted conventional radiotherapy schemes are used (daily fractions for almost nine weeks), tumor proliferation would be relevant during radiotherapy, achieving tumor repopulation during this very long treatment time and therefore, reducing tumor control induced by radiation (41). Furthermore, conventionally fractionated radiotherapy probably does not take full advantage of the increased radiosensitation observed when enzalutamide is given in the presence of fractions higher than 2 Gy (hypofractionated radiotherapy) (38).

We can conclude that the treatment schedule proposed here for the first time is safe and very active in reducing the PSA levels. Our study also showed that such a PSA reduction is maintained 6 months after the cessation of enzalutamide treatment. Longer follow-up is needed to confirm the potential use of this combination in future randomized trials.

DATA AVAILABILITY STATEMENT

The data presented in the study is available on request, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the CEIm University Hospital Canarias. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This is an independent academic study (Canarian Foundation of Health Investigations, FUNCANIS) supported by an unrestricted educational grant from Astellas.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.891886/full#supplementary-material

REFERENCES

1. NCCN. Prostate Cancer. *NCCN Guidelines Version 3* (2016). Available at: www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.
2. Gray PJ, Zietman AL. Dose-Escalated Radiotherapy for Prostate Cancer: Is the Sky the Limit? *JAMA Oncol* (2015) 1:883–4. doi: 10.1001/jamaoncol.2015.2419
3. Lee WR. Prostate Cancer and the Hypofractionation Hypothesis. *J Clin Oncol* (2013) 31:3849–51. doi: 10.1200/JCO.2013.52.4942
4. Zietman AL. Making Radiation Therapy for Prostate Cancer More Economical and More Convenient. *J Clin Oncol* (2016) 34:2323–4. doi: 10.1200/JCO.2016.67.3764
5. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfieldet D, et al. Conventional Versus Hypofractionated High- Dose Intensity-Modulated

Radiotherapy for Prostate Cancer: 5-Year Outcomes of the Randomised, non-Inferiority, Phase 3 CHHiP Trial. *Lancet Oncol* (2016) 17:1047–60.
6. Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer. *J Clin Oncol* (2016) 34:2325–32. doi: 10.1200/JCO.2016.67.0448
7. Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al. Randomized Trial of a Hypofractionated Radiation Regimen for the Treatment of Localized Prostate Cancer. *J Clin Oncol* (2017) 35:1884–90.
8. Jackson WC, Hartman HE, Dess RT, Soni PD, Hearn JWD, Reichert ZR, et al. Addition of Androgen-Deprivation Therapy or Brachytherapy Boost to External Beam Radiotherapy for Localized Prostate Cancer: A Network Meta-Analysis of Randomized Trials. *J Clin Oncol* (2020) 38:3024–31. doi: 10.1200/JCO.19.03217
9. Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen Deprivation Therapy: Progress in Understanding Mechanisms of Resistance and Optimizing Androgen Depletion. *Nat Clin Pract Urol* (2009) 6:76–85. doi: 10.1038/ncpuro1296
10. Isbarn H, Boccon-Gibod L, Carroll PR, Montorsi F, Schulman C, Smithet MR, et al. Androgen Deprivation Therapy for the Treatment of Prostate Cancer: Consider Both Benefits and Risks. *Eur Urol* (2009) 55:62–75. doi: 10.1016/j.eururo.2008.10.008
11. Keating NL, O'Malley AJ, Freedland SJ, Smithet MR. Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy: Observational Study of Veterans With Prostate Cancer. *J Natl Cancer Inst* (2010) 102:39–46. doi: 10.1093/jnci/djp404
12. Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnickal NM. Bone Loss After Initiation of Androgen Deprivation Therapy in Patients With Prostate Cancer. *J Clin Endocrinol Metab* (2005) 90:6410–7. doi: 10.1210/jc.2005-0183
13. Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MPCasodex Early Prostate Cancer Trialists' Group, et al. Antiandrogen Monotherapy in Patients With Localized or Locally Advanced Prostate Cancer: Final Results From the Bicalutamide Early Prostate Cancer Programme at a Median Follow-Up of 9. *7 Years BJU Int* (2010) 105(8):1074–81. doi: 10.1111/j.1464-410X.2010.09319.x
14. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation With or Without Antiandrogen Therapy in Recurrent Prostate Cancer. *N Engl J Med* (2017) 376:417–28.
15. Brower V. Bicalutamide With Radiotherapy for Prostate Cancer. *Lancet Oncol* (2017) 18(3):e141. doi: 10.1016/S1470-2045(17)30097-9
16. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer. *Science* (2009) 324:787–90.
17. Belikov S, Öberg C, Jääskeläinen T, Rahkama V, Palvimo JJ, Wrange Ö. FoxA1 Corrupts the Antiandrogenic Effect of Bicalutamide But Only Weakly Attenuates the Effect of MDV3100 (Enzalutamide™). *Mol Cell Endocrinol* (2013) 365:95–107. doi: 10.1016/j.mce.2012.10.002
18. Semenas J, Dizeyi N, Persson JL. Enzalutamide as a Second Generation Antiandrogen for Treatment of Advanced Prostate Cancer. *Drug Des Devel Ther* (2013) 7:875–81. doi: 10.2147/DDDT.S45703
19. Penson DF, Armstrong AJ, Concepcion R, Agarwal N, Olsson C, Karsh L, et al. Enzalutamide Versus Bicalutamide in Castration-Resistant Prostate Cancer: The STRIVE Trial. *J Clin Oncol* (2016) 34:2098–106. doi: 10.1200/JCO.2015.64.9285
20. Beer TM, Armstrong AJ, Rathkopf DA, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in Metastatic Prostate Cancer Before Chemotherapy. *New Eng J Med* (2014) 371:424–33. doi: 10.1056/NEJMc1410239
21. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in Men With Nonmetastatic , Castration-Resistant Prostate Cancer. *New Eng J Med* (2018) 378:2465–74. doi: 10.1056/NEJMoa1800536
22. Davis ID, Martin AJ, Stockler MRENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. Enzalutamide With Standard First-Line Therapy in Metastatic Prostate Cancer. *N Engl J Med* (2019) 381(2):121–31.
23. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol* (2019) 37(32):2974–86. doi: 10.1200/JCO.19.00799
24. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, et al. Enzalutamide Monotherapy in Hormone-Naive Prostate Cancer: Primary Analysis of an Open-Label, Single-Arm, Phase 2 Study. *Lancet Oncol* (2014) 15(6):592–600. doi: 10.1016/S1470-2045(14)70129-9
25. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel HV, Heidenreich A, et al. Long-Term Efficacy and Safety of Enzalutamide Monotherapy in Hormone Naïve Prostate Cancer: 1 and 2 Year Open-Label Follow Up Results. *Eur Urol* (2015) 68:787–94. doi: 10.1016/j.eururo.2015.01.027
26. Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel HV, Heidenreich A, et al. Long-Term Activity and Safety of Enzalutamide Monotherapy in Hormone Naïve Prostate Cancer: 3 Year Open Label Follow Up Results. *J Urol* (2018) 199:459–65. doi: 10.1016/j.juro.2017.08.103
27. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, et al. The Efficacy and Safety of Degarelix: A 12- Month, Comparative, Randomized, Open-Label, Parallel-Group Phase III Study in Patients With Prostate Cancer. *BJU Int* (2008) 102:1531–38. doi: 10.1111/j.1464-410X.2008.08183.x
28. Bolla M, Neven A, Maingon P, Carrie C, Boladeras A, Andreopoulos D, et al. Short Androgen Suppression and Radiation Dose Escalation in Prostate Cancer: 12-Year Results of EORTC Trial 22991 in Patients With Localized Intermediate-Risk Disease. *J Clin Oncol* (2021) 39(27):3022–33. doi: 10.1200/JCO.21.00855
29. Barrado M, Blanco-Luquin I, Navarrete PA, Visus I, Guerrero-Setas D, Escors D, et al. Radiopotentiation of Enzalutamide Over Human Prostate Cancer Cells as Assessed by Real-Time Cell Monitoring. *Rep Pract Oncol Radiother* (2019) 24(2):221–6. doi: 10.1016/j.rpor.2019.02.002
30. Ghashghaei M, Muanza T, Paliouras M, Niazi T. Effect of Enzalutamide on Sensitivity in Prostate Cancer Cells to Radiation by Inhibition of DNA Double Strand Break Repair. *J Clin Oncol* (2017) 35(6_suppl):208. doi: 10.1200/JCO.2017.35.6_suppl.208
31. Sekhar KR, Wang J, Freeman ML, Kirschner AN. Radiosensitization by Enzalutamide for Human Prostate Cancer is Mediated Through the DNA Damage Repair Pathway. *PLoS One* (2019) 14(4):e0214670. doi: 10.1371/journal.pone.0214670
32. Ghashghaei M, Niazi TM, Heravi M, Bekerat H, Trifiro M, Paliouras , et al. Enhanced Radiosensitization of Enzalutamide via Schedule Dependent Administration to Androgen-Sensitive Prostate Cancer Cells. *Prostate* (2018) 78(1):64–75. doi: 10.1002/pros.23445
33. Spratt DE, Malone S. Roy S Prostate Radiotherapy With Adjuvant Androgen Deprivation Therapy (ADT) Improves Metastasis-Free Survival Compared toNeoadjuvant ADT: An Individual Patient Meta-Analysis. *J Clin Oncol* (2021) 39(2):136–44. doi: 10.1200/JCO.20.02438
34. Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Hypofractionated Intensity-Modulated Radiotherapy (70 Gy at 2.5 Gy Per Fraction) for Localized Prostate Cancer: Cleveland Clinic Experience. *Int J Radiat Oncol Biol Phys* (2007) 68(5):1424– 30. doi: 10.1016/j.ijrobp.2007.01.067
35. Arraras Urdaniz JI, Villafranca Iturre E, Arias de la Vega F, Domínguez Domínguez MA, Lainez Milagro N, Manterola Burgaleta A, et al. The Eortc Quality of Life Questionnaire QLQ-C30 (Version 3.0). Validation Study for Spanish Prostate Cancer Patients. *Arch Esp Urol* (2008) 61(8):949–54. doi: 10.4321/S0004-06142008000800017
36. Arraras JI, Villafranca E, Arias de la Vega F, Romero P, Rico M, Vilaet M, et al. The EORTC Quality of Life Questionnaire for Patients With Prostate Cancer: EORTC QLQ-PR25. Validation Study for Spanish Patients. *Clin Transl Oncol* (2009) 11(3):160–4. doi: 10.1007/S12094-009-0332-z
37. R Core Team. *A: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing (2021). Available at: https://www.R-project.org/.
38. Kaplan I, Bubley GJ, Bhatt RS, Taplin ME, Dowling S, Mahoney K, et al. Enzalutamide With Radiation Therapy for Intermediate-Risk Prostate Cancer: A Phase 2 Study. *Int J Radiat Oncol Biol Phys* (2021) 110(5):1416–22. doi: 10.1016/j.ijrobp.2021.02.027
39. Arcangeli G, Saracino B, Arcangeli S, Gomellini S, Petrongari MG, Sanguineti G, et al. Moderate Hypofractionation in High-Risk, Organ-Confined Prostate Cancer: Final Results of a Phase III Randomized Trial. *J Clin Oncol* (2017) 35 (17):1891–7. doi: 10.1200/JCO.2016.70.4189

40. Tree A, Griffin C, Syndikus I, Birtle A, et al. Nonrandomized Comparison of Efficacy and Side Effects of Bicalutamide Compared With Luteinizing Hormone-Releasing Hormone (LHRH) Analogs in Combination With Radiation Therapy in the CHHiP Trial. *Int J Radiat Oncol Biol Phys* (2022) 113(2):305–15. doi: 10.1016/j.ijrobp.2021.12.160
41. Pedicini P, Strigari L, Benassi M. Estimation of a Self-Consistent Set of Radiobiological Parameters From Hypofractionated Versus Standard Radiation Therapy of Prostate Cancer. *Int J Radiat Oncol Biol Phys* (2013) 85(5):e231–7. doi: 10.1016/j.ijrobp.2012.11.033

Conflict of Interest: PL received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Carl-Zeiss and support for attending meetings and/or travel from Carl-Zeiss. JR-M received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ASTELLAS, BAYER, JANSSEN, CASEN-RECORDATI, IPSEN PHARMA & BOSTON SCIENTIFIC and support for attending meetings and/or travel from ASTELLAS & JANSSEN. He also received equipment, materials, drugs, medical writing, gifts or other services from ASTELLAS, BAYER, JANSSEN, CASEN-RECORDATI, IPSEN PHARMA & BOSTON SCIENTIFIC. AP-E received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ASTELLAS, JANSSEN & IPSEN PHARMA and support for attending meetings and/or travel from ASTELLAS & JANSSEN. AL declared payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ASTELLAS, JANSSEN & IPSEN PHARMA and declared participation on a Data Safety Monitoring Board or Advisory Board JANSSEN & ASTELLAS. EV received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from JANSSEN &IPSEN PHARMA, support for attending meetings and/or travel from ELEKTA, and declared participation on a Data Safety Monitoring Board or Advisory Board for JANSSEN. She is also the National Coordinator of the Brachytherapy Group of the Spanish Society of Radiation Oncology (SEOR). AG-I received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from ASTELLAS, BAYER, JANSSEN, IPSEN PHARMA & BOSTON SCIENTIFIC and declared participation on a Data Safety Monitoring Board or Advisory Board for BAYER, ELEKTA, JANSSEN & ASTELLAS. GS received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from ASTELLAS, BAYER & JANSSEN and support for attending meetings and/or travel from ASTELLAS & IPSEN PHARMA. XM received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from ASTELLAS & BAYER and support for attending meetings and/or travel from ASTELLAS, IPSEN PHARMA & JANSSEN. He declared Participation on a Data Safety Monitoring Board or Advisory Board for BAYER &ASTELLAS. The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Oncology

ORIGINAL RESEARCH
published: 14 July 2022
doi: 10.3389/fonc.2022.880042

Intraindividual Comparison Between [^{18}F] PSMA-1007 PET/CT and Multiparametric MRI for Radiotherapy Planning in Primary Prostate Cancer Patients

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Introduction: Accurate detection and segmentation of the intraprostatic gross tumor volume (GTV) is pivotal for radiotherapy (RT) in primary prostate cancer (PCa) since it influences focal therapy target volumes and the patients' cT stage. The study aimed to compare the performance of multiparametric resonance imaging (mpMRI) with [^{18}F] PSMA-1007 positron emission tomography (PET) for intraprostatic GTV detection as well as delineation and to evaluate their respective influence on RT concepts.

Materials and Methods: In total, 93 patients from two German University Hospitals with [^{18}F] PSMA-1007-PET/CT and MRI (Freiburg) or [^{18}F] PSMA-1007-PET/MRI (Dresden) were retrospectively enrolled. Validated contouring techniques were applied for GTV-PET and -MRI segmentation. Absolute tumor volume and cT status were determined for each imaging method. The PCa distribution from histopathological reports based on biopsy cores and surgery specimen was used as reference in terms of laterality (unilateral *vs*. bilateral).

Results: In the Freiburg cohort (n = 84), mpMRI and PET detected in median 2 (range: 1–5) and 3 (range: 1–8) GTVs, respectively ($p < 0.01$). The median GTV-MRI was significantly smaller than the GTV-PET, measuring 2.05 *vs*. 3.65 ml ($p = 0.0005$). PET had a statistically significant higher concordance in laterality with surgery specimen compared to mpMRI ($p = 0.04$) and biopsy ($p < 0.01$), respectively. PSMA PET led to more cT2c and cT3b stages, whereas cT3a stage was more pronounced in mpMRI. Based on the cT stage derived from

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Edited by:
Tonghe Wang,
Emory University, United States

Reviewed by:
Cem Onal,
Başkent University, Turkey
Siroos Mirzaei,
Wilhelminen Hospital, Austria
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Specialty section:
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

Received: 20 February 2022
Accepted: 25 May 2022
Published: 14 July 2022

Citation:
Marinescu IM, Spohn SKB, Kiefer S, Bronsert P, Ceci L, Holzschuh J, Sigle A, Jilg CA, Rühle A, Sprave T, Nicolay NH, Winzer R, Rehm J, Kotzerke J, Hölscher T, Grosu AL, Ruf J, Benndorf M and Zamboglou C (2022) Intraindividual Comparison Between [^{18}F] PSMA-1007 PET/CT and Multiparametric MRI for Radiotherapy Planning in Primary Prostate Cancer Patients. Front. Oncol. 12:880042. doi: 10.3389/fonc.2022.880042

mpMRI and PET information, 21 and 23 as well as 59 and 60 patients, respectively, were intermediate- and high-risk according to the National Comprehensive Cancer Network (NCCN) v1.2022 criteria. In the Dresden cohort (n = 9), similar results were observed.

Conclusion: Intraprostatic GTV segmentation based on [18F] PSMA-1007 PET results in more and larger GTVs compared to mpMRI. This influences focal RT target volumes and cT stage definition, but not the NCCN risk group.

Keywords: positron-emission tomography, multiparametric MRI, radiation therapy, prostate cancer, PSMA

INTRODUCTION

Accurate detection and segmentation of the intraprostatic gross tumor volume (GTV) is pivotal for definitive radiotherapy (RT) in patients with primary prostate cancer (PCa). First, the intraprostatic tumor volume and its extension (*e.g.*, infiltration of the seminal vesicles) may affect the patients' cT stage and thus the patients' individual risk group. Consequently, it affects the RT concepts in terms of androgen deprivation therapy (ADT) administration and clinical target volumes (CTVs). Second, a precise intraprostatic GTV definition is of importance for focal RT. Interest for this has been gained in the last years since its thorough coverage is a prerequisite for successful focal RT approaches. Currently, multiparametric magnetic resonance imaging (mpMRI) is the gold standard for intraprostatic GTV detection and segmentation (1). However, previous studies suggested that mpMRI underestimates true GTV volume and misses clinically significant lesions (2–4). In parallel, positron emission tomography with prostate-specific membrane antigen (PSMA)-labeled tracers has emerged as a valuable technique for staging primary and recurrent PCa (5–8).

The current study aimed to (i) compare the performance of mpMRI with [^{18}F] PSMA-1007 PET for intraprostatic GTV detection as well as delineation in patients with primary PCa and to (ii) evaluate their respective influence on RT concepts. Therefore, patients from two German university hospitals were included, and validated contouring techniques were applied for GTV segmentation (5, 9). Additionally, histology information was considered as the standard of reference by considering the PCa laterality in surgery specimen and prostate biopsy cores.

MATERIALS AND METHODS

Patients

This study consists of patients from two university hospitals in Germany:

(1) Center 1, Freiburg: In total, 84 patients with biopsy-proven primary adenocarcinoma of the prostate who underwent [^{18}F] PSMA-1007 PET/CT and 3-tesla MR imaging before any therapy (53 patients received a primary RT, 29 patients underwent open or robot-assisted prostatectomy, and three patients received androgen deprivation therapy +/- docetaxel chemotherapy) were retrospectively enrolled. The exclusion criteria were defined as any therapeutic interventions prior to imaging (such as androgen deprivation therapy or previous transurethral prostate resection) and a time difference between the PSMA PET and the MRI scan greater than 120 days. Additionally, information regarding tumor laterality was extracted based on biopsy cores and surgery specimen (unilateral *vs.* bilateral). The data was available in the form of histopathological or tumor board reports. The institutional review board of the Albert-Ludwigs-University Freiburg (Germany) approved the study (no. 476/19) (please see **Table 1** for the detailed patients' characteristics).

(2) Center 2, Dresden: Nine patients with biopsy-confirmed primary prostate cancer who received [^{18}F] 1007-PSMA PET/MRT before therapy were recruited retrospectively. Any therapeutic procedures performed before imaging were defined as exclusion criteria. The inclusion criteria were histopathologically confirmed primary prostate cancer, a pre-treatment [^{18}F] 1007-PSMA PET/MRI scan, and a scheduled radical prostatectomy. Between June 2020 and October 2021, 9 patients were enrolled retrospectively (please refer to **Table 1** for the patients' characteristics). All patients provided written informed consent.

MR Imaging

Center 1, Freiburg: *In vivo* prostate MRI was performed with 3-tesla magnets (MAGNETOM Trio Tim, MAGNETOM Skyra, MAGNETOM Vida; all Siemens, Germany). For image acquisition, no endorectal coil was used. In all patients, at least biplanar T2-weighted imaging and diffusion-weighted imaging were performed. Additionally, a very high b-value image was extrapolated with b = 1,400 s/mm^2 following PI-RADS recommendations. Dynamic contrast-enhanced images were acquired in the patients examined with Skyra and Vida (please see our previous publication for a more detailed information on our MR imaging protocols) (10).

PET Imaging

Center 1, Freiburg: [^{18}F] PSMA-1007 had been synthesized according to Cardinale et al. (11). The patients underwent a

Abbreviation: T2w, biplanar T2 weighted imaging; ADC, Apparent diffusion coefficient;GTV, gross tumour volume; PCa, prostate cancer; PSMA PET, prostate-specific membrane antigen positron-emission tomography; mpMRI, multiparametric magnetic resonance imaging R, right. T2w, biplanar T2 weighted imaging; ADC, Apparent diffusion coefficient;GTV, gross tumour volume; PCa, prostate cancer; PSMA PET, prostate-specific membrane antigen positron-emission tomography; mpMRI, multiparametric magnetic resonance imaging R, right.

TABLE 1 | Patients' characteristics.

Freiburg cohort	
Patients, *n*	84
Median age in years (range)	69.5 (49–90)
Median PSA before imaging, ng/ml (range)	11.95 (0.7–159)
Median time gap between mpMRI and PSMA-PET in days (range)	34 (0–114)
Gleason Score in biopsy cores, *n*	
6	4
7a	28
7b	26
8	16
9	8
10	1
Unknown	1
Patients with available information on biopsy cores, *n*	83
Median percent of positive biopsy cores (range)	33.33 (3.33–100)
Patients with available information on surgery specimen, *n*	28
Dresden cohort	
Patients, *n*	9
Median age in years (range)	68 (58–80)
Median PSA before imaging, ng/ml (range)	30.3 (6.5–126)
Gleason Score in biopsy cores	
6	0
7a	3
7b	2
8	1
9	1
10	1

whole-body PET scan starting 2 h after injection (median activity in megaBecquerel: 313 MBq, range: 245–454 MBq). The scans were performed with a 64-slice Vereos PET/CT scanner in 61 patients and with a Gemini TF Big Bore in 23 patients (Philips Healthcare, USA). During the PET scan, a contrast-enhanced diagnostic CT scan (120 kVp, 100–400 mAs, dose modulation) was performed. The tracer uptake was quantified using standardized uptake values (SUV) normalized body weight.

PET/MR Imaging

Center 2, Dresden: The preparation followed a standard protocol. 18F-PSMA was administered intravenously. The time between 18F-PSMA injection and PET/MRI was 1.5 h. PET/MRI was performed on a 3-T scanner with the patients in supine position, arms by the sides (Ingenuity TF PET/MR; Philips Health Systems, Amsterdam, Netherlands). Nine to ten bed positions with an overlap of 9 cm were acquired, with a scan time of 2 min each. The field-of-view was 18 cm, and the reconstructed isotropic spatial resolution was 5.5 mm. From the head to the distal femur (integrated quadrature body coil), low-resolution T1-weighted fast-field-echo images were acquired to create a map for attenuation correction *via* segmentation into three tissue classes (air, lung, and soft tissue), followed by the assignment of respective attenuation values. The patient's position was maintained throughout the procedure to ensure optimal co-registration, and PET was performed immediately following the attenuation scan. MRI was performed according to the treatment center's standard protocol for pelvic MRI in the follow-up of pelvic malignancy. Thus, all pelvic MRIs included T2-weighted, diffusion-weighted, and T1-weighted contrast-enhanced sequences (Sense-Xl-Torso coil). Apparent diffusion coefficient (ADC) maps were generated automatically. Contrast-enhanced sequences were performed about 60 s after the intravenous administration of 0.2 ml gadolinium diethylenetriamine penta-acetic acid or 0.1 ml gadobutrol per kilogram of body weight (Magnevist®/Gadovist®, Bayer Pharma, Berlin, Germany), followed by 20 ml saline. Philips Fusion Viewer software was used to create merged PET/MR images, including multiplanar reconstructions.

Image Delineation

One board-certified radiologist (MB) and one board-certified radiation oncologist (CZ) with >6 years of experience in interpretation of prostate MRI delineated all areas suspicious for a clinically significant tumor in the axial T2w sequences (GTV-MRI) in consensus. For delineation of T2w images, DWI (including the extrapolated *b*-value image) and ADC maps were available. Standardized imaging criteria (PI-RADSv2.1) were applied for tumor delineation. Lesions with a PI-RADS category ≥3 were considered positive.

Two radiation oncologists with 6 (CZ) and 1–3 years (MM or SP) of experience in interpretation of PSMA-PET images, respectively, contoured GTV-PET in consensus by applying a PET image windowing from SUVmin–max 0–10 (9) in Eclipse v15.1 software (Varian Medical Systems, USA). The presence of PCa on PET images was defined as mono- or multifocal uptake greater than the adjacent background in more than one slice (GTV-PET) (9). Apart from PET and CT images for anatomical orientation, no additional clinical information was provided.

The prostate volume on CT and MR images was delineated by an experienced reader (CZ) according to the ESTRO-ACROP guidelines (12).

Statistical Analysis

The statistical analysis was performed on GraphPad Prism v8.4.2 (GraphPad Software, USA). Normal distribution was tested using the D'Agostino and Pearson normality test. A Wilcoxon matched-pairs signed rank test was used to compare not normally distributed metric variables. For normally distributed metric variables, a paired *t*-test was used for comparison. For categorical variables, one-sided Fisher's exact test was used. The significance level was defined as 0.05 (the figures were created on GraphPad Prism v8.4.2, GraphPad Software, USA).

RESULTS

Freiburg Cohort

In the entire cohort (n = 84), 144 and 245 intraprostatic GTVs were detected by mpMRI and PET, respectively. On a patient basis, mpMRI and PET detected in median 2 (range: 1–5) and 3 (range: 1–8) GTVs, respectively ($p < 0.01$) (**Figure 1**). The median volume of GTV-MRI and GTV-PET per patient was 2.1 ml (range: 0.2–42.8) and 3.7 ml (range: 0.4–85), respectively ($p < 0.01$)

(**Figure 1**). The distribution of the cT stages based on mpMRI and PSMA PET is represented in **Figure 2**. PSMA PET led to more cT2c (23 *vs.* 17 patients) and cT3b (25 *vs.* 10 patients) stages, whereas cT3a stage was more pronounced in mpMRI (47 vs. 32 patients). Based on the cT stage derived from mpMRI and PET information, 4 (5%) and 1 (1%), 21 (25%) and 23 (27%), and 59 (70%) and 60 (71%) patients were of low, intermediate, and high risk according to the national comprehensive cancer network (NCCN) v1.2022 criteria.

PCa distribution from histopathological reports based on biopsy cores and surgery specimen was available in 64 and 28 patients, respectively. First, PCa laterality on biopsy cores was considered: MRI and PSMA showed concordance in 46 patients (66%) and 44 patients (63%), respectively (p = 0.86). In 10 patients, solely MR imaging was concordant in PCa laterality with biopsy cores, whereas PET was not. On the contrary, PET was concordant in 8 patients, in which MRI was not. Considering the combined PET and MR information, 36 patients (51%) had concordance in laterality with the biopsy specimen. In the subgroup of patients with bilateral PCa lesions according to biopsy samples, the following were observed: MRI and PET were concordant with biopsy cores in 37 (82%) and 42 (93%) patients, respectively ($p < 0.01$). In this case, MRI was coincident with the biopsy cores in 1 patient, where PSMA was not and PSMA in 6 patients, where MRI was not (**Figure 3**).

Second, the PCa laterality on surgery specimen was analyzed, and mpMRI and PET were in 20 (71%) and 26 (93%) of patients, congruent with the surgery specimen, respectively. PET had a statistically significant higher concordance in laterality with surgery specimen compared to mpMRI (p = 0.04). Third, the pT stage in surgery specimen was compared with cT stage based on PET and mpMRI, respectively. The cT stage based on mpMRI and PET was concordant with pT stage in 16 (57%) and 18 (64%) patients, respectively. **Figure 4** illustrates an example of the discordant findings between MR and PSMA PET.

Dresden Cohort

The median volume of GTV-MRI and GTV-PET per patient was 3.8 ml (range: 0.1–59.5) and 4.4 ml (range: 2.1-60.1), respectively (p = 0.02). According to mpMRI and PET, 1 and 3 patients had cT3b stage, and 4 and 3 patients had cT3a stage, respectively. Five and 6 patients were high-risk according to the NCCN criteria v1.2022 in mpMRI and PET, respectively.

Pooled Database

Finally, the pooled data from all patients (n = 93) was analyzed. The median volume of GTV-MRI and GTV-PET was 2.2 ml (range: 0.1–59.5) and 3.7 ml (range: 0.4–85), respectively ($p < 0.0001$). According to mpMRI and PET, 9 and 1 patients had cT2a stage, 20 and 26 had cT2c stage, 51 and 35 patients had cT3a stage, and 11 and 28 patients had cT3b stage, respectively (**Table 2**).

DISCUSSION

Several studies compared [^{68}Ga]-labeled PSMA tracers with the current standard-of-care mpMRI for intraprostatic GTV detection (13–15) and segmentation (5, 16, 17) by using histopathology derived from biopsy cores or from surgery specimen as the standard of reference. All studies concluded that [^{68}Ga]-PSMA PET imaging provides complementary information. However, our group reported that visual [^{68}Ga]-PSMA-11 PET image interpretation misses clinically relevant PCa in terms of microscopic lesions with ISUP grade >1 in approximately 30% of patients (18). Furthermore, in their study, Kuten et al. performed a head-to-head comparison between [^{18}F] PSMA-1007 and [^{68}Ga] PSMA-11 PET/CT and reported similar results for both tracers, with better performance for the [^{18}F] PSMA-1007 tracer in less intense foci (19). The prospective ProStaPET study compared [^{18}F] DCFPyL PET and mpMRI for PCa detection by using histopathology after surgery as reference (20). The authors concluded that combined PET/MR information does not outperform mpMRI information alone. However, no dedicated segmentation process was performed in the latter trial. Consequently, we initiated this study to compare [18F] PSMA-1007 PET/CT with mpMRI for intraprostatic GTV detection and delineation using validated segmentation

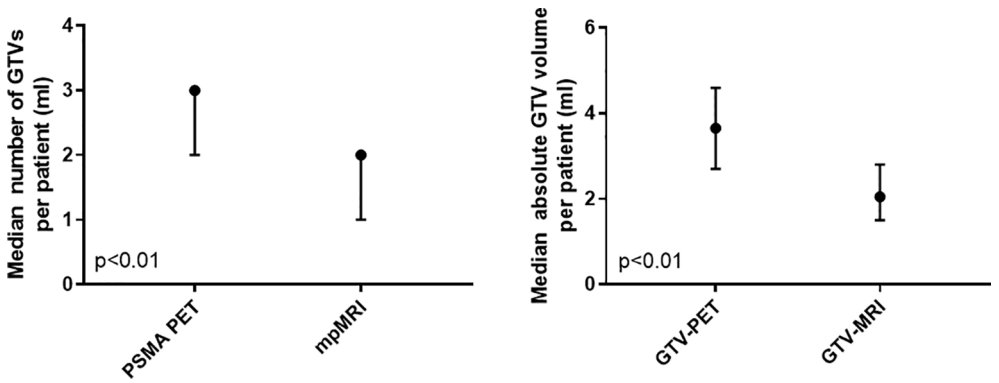

FIGURE 1 | Number and absolute gross tumor volumes in mpMRI and PSMA PET on a patient basis in the entire cohort (n = 84). The median value and the 95% confidence interval are represented. PSMA PET, prostate-specific membrane antigen positron-emissions tomography; mpMRI: multiparametric magnetic resonance imaging.

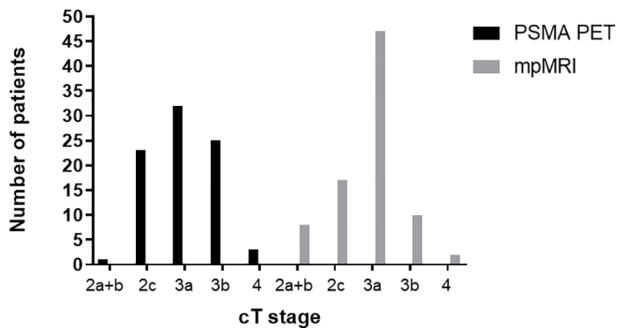

FIGURE 2 | Comparison of cT stage based on PSMA PET and mpMRI in the entire cohort (n = 84). PSMA PET, prostate-specific membrane antigen positron-emissions tomography; mpMRI, multiparametric magnetic resonance imaging.

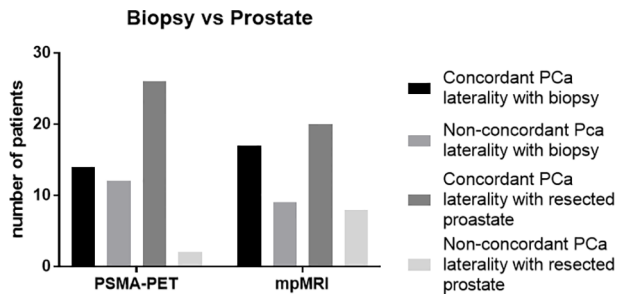

FIGURE 3 | Concordance of prostate cancer laterality with biopsy (n = 64) and resected prostate (n = 28), respectively. The absolute numbers of patients are represented. PSMA PET, prostate-specific membrane antigen positron-emission tomography; mpMRI, multiparametric magnetic resonance imaging.

techniques and histopathology as the standard of reference in a subgroup of patients.

The first aim of our study was to analyze the value of [^{18}F] PSMA-1007 PET and mpMRI for focal RT approaches. Focal RT can be applied in three ways: ultra-focal (RT of the PCa lesion), on a half-gland basis [RT of the gland including PCa lesion(s)], and localized (RT of the entire prostate with dose escalation to the PCa lesion(s) (21). A high-dose coverage of the intraprostatic GTV is warranted for all focal RT approaches to increase the tumor control probability (22). In the Freiburg cohort, PET detected significantly more intraprostatic PCa lesions with a significantly larger volume than mpMRI. The PET-derived GTV was also significantly larger in an external cohort. These findings are in concordance with previous studies which compared [^{68}Ga]-labeled PSMA tracers with mpMRI (13–15). Taken together, the findings of our study suggest that [^{18}F] PSMA-1007 is a promising tool for focal therapy guidance to intraprostatic GTVs and might outperform the stand-alone MRI. However, mpMRI should not be omitted in this context since it provides complementary information in some of the patients since no PSMA expression was reported in approximately 10% of intraprostatic GTVs (23, 24). In line with this, in our study, MR showed concordance with biopsy PCa distribution in 12% of patients in which PET failed to detect the correct distribution. In addition, it is a useful tool to delineate the prostate and the urethra during focal RT planning (25). One must consider that the implementation of PSMA PET imaging leads to larger RT volumes and a decrease in specificity. Parts of non-PCa tissue within the prostate might likewise be irradiated, which might lead to an increased risk for toxicity. Whether a RT dose escalation on GTVs based on combined PSMA PET and mpMR information is safe and increases the tumor control will be examined by the randomized controlled HypoFocal-SBRT trial in the future (26). Interestingly, PET had even a higher concordance in laterality of PCa lesion with surgery specimen compared to mpMRI and biopsy cores. This finding is crucial for half-gland RT approaches (27), as it suggests that PSMA PET should also be incorporated in this clinical scenario to decrease the risk of false-negative findings in mpMRI and biopsies.

The second aim was to compare both imaging modalities for cT stage definition in primary PCa patients. Currently, the cT stage is determined by digital rectal examination (DRE). The cT stage impacts the patients' NCCN risk groups and consequently affects treatment concepts in terms of CTV margins (12) and ADT administration (28). In both study cohorts, PSMA PET detected more bilateral lesions and more seminal vesicle involvement than mpMRI. Seminal vesicle involvement in PET may influence RT margins in terms of a cephalad expansion of the CTV margins. In contrast, more patients had an extracapsular extension in mpMR images. The latter result is not surprising since a proper evaluation of the prostatic capsule is difficult in PET/CT due to the low soft tissue contrast of CT imaging. However, this finding might also affect RT margins by expansion of the CTV in the area of the extracapsular extension. Privé et al. compared [^{18}F] PSMA-1007 PET with mpMRI by using histopathological outcome in surgery specimen as the standard of reference in 23 patients and observed comparable results (29). Nevertheless, the resulting NCCN risk groups of the patients in our study were comparable between mpMRI and PSMA. Thus, ADT concepts may not be affected by the usage of additional PET imaging. cT stage based on PET or mpMRI had only moderate concordance (57–64% of patients) with pT stage in a surgery specimen. Future studies should assess whether cT stage based on mpMRI and PSMA PET outperforms the cT stage based on DRE in terms of prognostic value for primary PCa patients.

In the following, we want to discuss the limitations of our study. First, since PET/CT scans are mainly conducted for primary PCa patients with advanced disease status, our study cohort consists primarily of patients with intermediate- and high-risk PCa. Thus, it is unclear whether our findings can be translated to low-risk PCa patients. However, low-risk patients are also suitable for ultra-focal therapies as an alternative to active surveillance. Therefore, the accuracy of PSMA-PET should be further evaluated in this patient group.

Second, the retrospective design of the study represents another limitation. Especially in the Freiburg cohort, histopathological reports from biopsy cores were available in only 64 patients (76%). Moreover, histopathology information

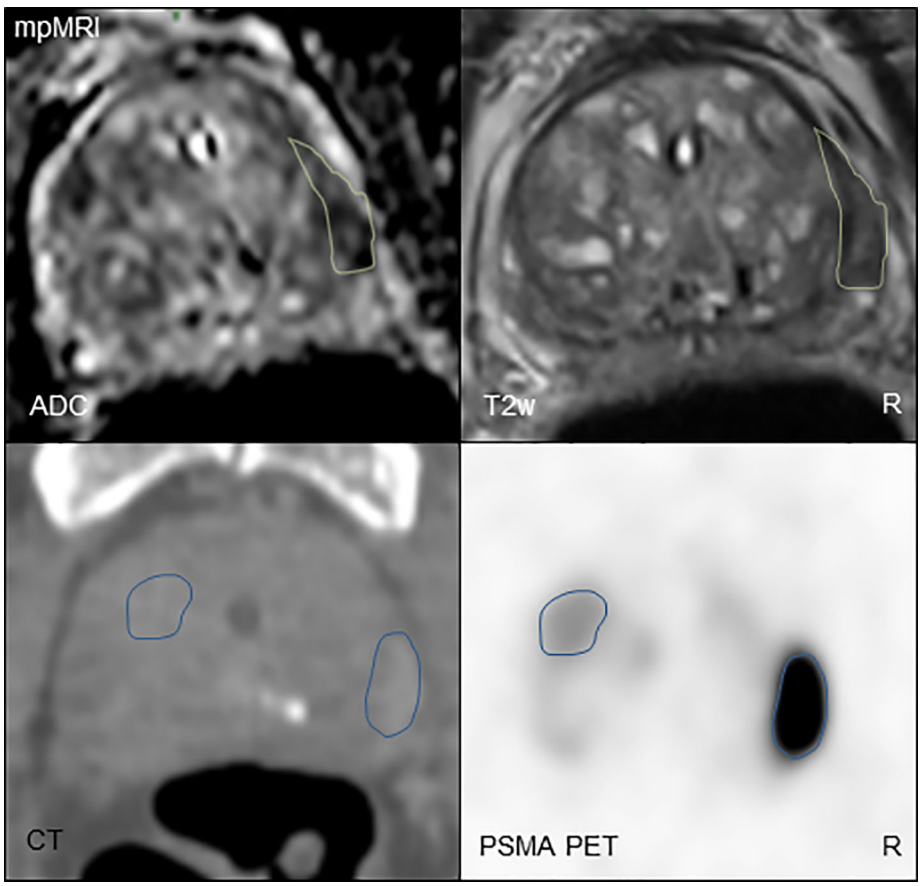

FIGURE 4 | Comparison of mpMRI (above) and PSMA PET (below) imaging in a PCa patient. For mpMRI, the biplanar T2-weighted imaging and diffusion-weighted imaging are shown. For the PSMA PET (PET image windowing: SUV 0–10), the CT scan is shown for anatomical orientation. The GTVs are displayed in green (GTV-MRI) and blue (PSMA PET), respectively. GTV-MRI was smaller than GTV-PET with 1.3 and 4.9 ml, respectively. mpMRI was concordant in PCa laterality with biopsy cores (unilateral, right), whereas PSMA PET showed concordance with surgery specimen (bilateral). T2w, biplanar T2-weighted imaging; ADC, apparent diffusion coefficient; GTV, gross tumor volume; PCa, prostate cancer; PSMA PET, prostate-specific membrane antigen positron-emission tomography; mpMRI, multiparametric magnetic resonance imaging; R, right.

from a surgery specimen was only available in 28 patients (33%), and histopathology information was not registered with the PET and mpMR information as was done in previous studies (4, 10). Thus, the comparison with standard-of-reference PCa in histopathology was performed on a laterality level. In the Dresden cohort, no reports were available.

Third, in particular for MR-based intraprostatic GTV contouring, an interobserver heterogeneity was reported (9,). To tackle this issue, this study implemented consensus contours from two experienced readers.

Finally, in the Freiburg cohort PET/CT and mpMRI scans were not acquired simultaneously with a median time gap between both examinations of 34 days. We addressed this issue by implementing an external cohort of patients with hybrid [^{18}F] PSMA-1007 PET/MR examinations. In this context, it should be mentioned that slightly different post-injection times were used in both centers (Freiburg: 2 h and Dresden: 1.5 h) which might hamper comparability.

Given the limitations of the research in our study and other studies (18) and considering the different concordance of both imaging methods with the histologic reference, ultra-focal radiotherapy targeting solely the PCa lesion should be further investigated in controlled clinical studies.

TABLE 2 | Pooled data of all patients.

All patients	Median/*n*		*P*-value
	mpMRI	PSMA PET	
GTV (ml)	2.2	3.7	<0.0001
cT	9	1	<0.0001
T2a	0	0	
T2b	20	26	
T2c	51	35	
T3a	11	28	
T3b	0	0	
T4			

CONCLUSION

In this study, we performed an intraindividual comparison between [18F] PSMA-1007 PET/CT and mpMRI in a large cohort of patients in two different university hospitals in Germany. Using validated contouring approaches, [18F] PSMA-1007 PET showed more and larger intaprostatic tumor lesions than MRI and detected more cT2c and cT3b stages. Additionally, PET had a statistically significant higher concordance in laterality with a surgery specimen compared to mpMRI ($p = 0.04$) and biopsy ($p < 0.01$), respectively. However, MRI identified more cT3a stages and provided complementary information in >10% of patients concerning PCa localization. These findings have an effect on the volume of focal RT targets and the definition of cT stages, but not on the NCCN risk group. Consequently, both image modalities should be used for the RT planning process on primary PCa patients. Prospective trials are currently ongoing to evaluate the safety and therapeutic efficacy of focal RT using combined PSMA PET and mpMRI data.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the Albert-Ludwigs-University Freiburg (Germany) (no. 476/19). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology: CZ, IMM, ALG, JRuf, MB. Patient recruitment: IMM, SKBS, CZ, AS, SK, PB, AS, CAJ. Data curation: CZ, ALG, SKBS. Writing—original draft preparation: CZ, IMM. Writing—review and editing, all, Supervision: ALG, JRuf, MB. Project administration: CZ. Visualization: JH, LC, AR, TS, NHN, RW, JRehm, JK, TH. All authors have read and agreed to the published version of the manuscript.

FUNDING

This study was part of the ERA PerMed JTC2018 project "PersoProCaRisk".

REFERENCES

1. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* (2018) 378(19):1767–77. doi: 10.1056/NEJMoa1801993
2. Priester A, Natarajan S, Khoshnoodi P, Margolis DJ, Raman SS, Reiter RE, et al. Magnetic Resonance Imaging Underestimation of Prostate Cancer Geometry: Use of Patient Specific Molds to Correlate Images With Whole Mount Pathology. *J Urol* (2017) 197(2):320–6. doi: 10.1016/j.juro.2016.07.084
3. Johnson DC, Raman SS, Mirak SA, Kwan L, Bajgiran AM, Hsu W, et al. Detection of Individual Prostate Cancer Foci *via* Multiparametric Magnetic Resonance Imaging. *Eur Urol* (2019) 75(5):712–20. doi: 10.1016/j.eururo.2018.11.031
4. Kramer M, Spohn SKB, Kiefer S, Ceci L, Sigle A, Oerther B, et al. Isotropic Expansion of the Intraprostatic Gross Tumor Volume of Primary Prostate Cancer Patients Defined in MRI-A Correlation Study With Whole Mount Histopathological Information as Reference. *Front Oncol* (2020) 10:596756. doi: 10.3389/fonc.2020.596756
5. Bettermann AS, Zamboglou C, Kiefer S, Jilg CA, Spohn S, Kranz-Rudolph J, et al. [(68)Ga-]PSMA-11 PET/CT and Multiparametric MRI for Gross Tumor Volume Delineation in a Slice by Slice Analysis With Whole Mount Histopathology as a Reference Standard - Implications for Focal Radiotherapy Planning in Primary Prostate Cancer. *Radiother Oncol* (2019) 141:214–9. doi: 10.1016/j.radonc.2019.07.005
6. Eder M, Neels O, Müller M, Bauder-Wüst U, Remde Y, Schäfer M, et al. Novel Preclinical and Radiopharmaceutical Aspects of [68Ga]Ga-PSMA-HBED-CC: A New PET Tracer for Imaging of Prostate Cancer. *Pharm (Basel Switzerland)*. (2014) 7(7):779–96. doi: 10.3390/ph7070779
7. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-Specific Membrane Antigen PET-CT in Patients With High-Risk Prostate Cancer Before Curative-Intent Surgery or Radiotherapy (proPSMA): A Prospective, Randomised, Multicentre Study. *Lancet (London England)*. (2020) 395(10231):1208–16. doi: 10.1016/S0140-6736(20)30314-7
8. Spohn S, Jaegle C, Fassbender TF, Sprave T, Gkika E, Nicolay NH, et al. Intraindividual Comparison Between (68)Ga-PSMA-PET/CT and mpMRI for Intraprostatic Tumor Delineation in Patients With Primary Prostate Cancer: A Retrospective Analysis in 101 Patients. *Eur J Nucl Med Mol Imaging* (2020) 47(12):2796–803. doi: 10.1007/s00259-020-04827-6
9. Spohn SKB, Kramer M, Kiefer S, Bronsert P, Sigle A, Schultze-Seemann W, et al. Comparison of Manual and Semi-Automatic [(18)F]PSMA-1007 PET Based Contouring Techniques for Intraprostatic Tumor Delineation in Patients With Primary Prostate Cancer and Validation With Histopathology as Standard of Reference. *Front Oncol* (2020) 10:600690. doi: 10.3389/fonc.2020.600690
10. Zamboglou C, Kramer M, Kiefer S, Bronsert P, Ceci L, Sigle A, et alThe Impact of the Co-Registration Technique and Analysis Methodology in Comparison Studies Between Advanced Imaging Modalities and Whole-Mount-Histology Reference in Primary Prostate Cancer. *Sci Rep* (2021) 11 (1):5836.
11. Cardinale J, Martin R, Remde Y, Schäfer M, Hienzsch A, Hübner S, et al. Procedures for the GMP-Compliant Production and Quality Control of [(18) F]PSMA-1007: A Next Generation Radiofluorinated Tracer for the Detection of Prostate Cancer. *Pharm (Basel Switzerland)* (2017) 10(4):77. doi: 10.3390/ph10040077
12. Salembier C, Villeirs G, De Bari B, Hoskin P, Pieters BR, Van Vulpen M, et al. ESTRO ACROP Consensus Guideline on CT- and MRI-Based Target Volume Delineation for Primary Radiation Therapy of Localized Prostate Cancer. *Radiother Oncol J Eur Soc Ther Radiol Oncol* (2018) 127(1):49–61. doi: 10.1016/j.radonc.2018.01.014
13. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous (68)Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. *Eur Urol.* (2016) 70(5):829–36. doi: 10.1016/j.eururo.2015.12.053

14. Chen M, Zhang Q, Zhang C, Zhao X, Marra G, Gao J, et al. Combination of (68)Ga-PSMA PET/CT and Multiparametric MRI Improves the Detection of Clinically Significant Prostate Cancer: A Lesion-By-Lesion Analysis. *J Nucl Med* (2019) 60(7):944–9. doi: 10.2967/jnumed.118.221010
15. Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, et al. The Additive Diagnostic Value of Prostate-Specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study. *Eur Urol* (2021) 80(6):682–9. doi: 10.1016/j.eururo.2021.08.002
16. Spohn S, Jaegle C, Fassbender TF, Sprave T, Gkika E, Nicolay NH, et al. Intraindividual Comparison Between Ga-68-PSMA-PET/CT and mpMRI for Intraprostatic Tumor Delineation in Patients With Primary Prostate Cancer: A Retrospective Analysis in 101 Patients. *Eur J Nucl Med Mol I.* (2020) 47 (12):2796–803. doi: 10.1007/s00259-020-04827-6
17. Zamboglou C, Drendel V, Jilg CA, Rischke HC, Beck TI, Schultze-Seemann W, et al. Comparison of (68)Ga-HBED-CC PSMA-PET/CT and Multiparametric MRI for Gross Tumour Volume Detection in Patients With Primary Prostate Cancer Based on Slice by Slice Comparison With Histopathology. *Theranostics.* (2017) 7(1):228–37. doi: 10.7150/thno.16638
18. Zamboglou C, Bettermann AS, Gratzke C, Mix M, Ruf J, Kiefer S, et al. Uncovering the Invisible-Prevalence, Characteristics, and Radiomics Feature-Based Detection of Visually Undetectable Intraprostatic Tumor Lesions in (68)GaPSMA-11 PET Images of Patients With Primary Prostate Cancer. *Eur J Nucl Med Mol Imaging.* (2021) 48(6):1987–97. doi: 10.1007/s00259-020-05111-3
19. Kuten J, Fahoum I, Savin Z, Shamni O, Gitstein G, Hershkovitz D, et al. Head-To-Head Comparison of (68)Ga-PSMA-11 With (18)F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. *J Nucl Med* (2020) 61(4):527–32. doi: 10.2967/jnumed.119.234187
20. Bodar YJL, Zwezerijnen B, van der Voorn PJ, Jansen BHE, Smit RS, Kol SQ, et al. Prospective Analysis of Clinically Significant Prostate Cancer Detection With [(18)F]DCFPyL PET/MRI Compared to Multiparametric MRI: A Comparison With the Histopathology in the Radical Prostatectomy Specimen, the ProStaPET Study. *Eur J Nucl Med Mol Imaging* (2022) 49 (5):1731–42. doi: 10.1007/s00259-021-05604-9
21. Kerkmeijer LGW, Groen VH, Pos FJ, Haustermans K, Monninkhof EM, Smeenk RJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. *J Clin Oncol* (2021) 39(7):787–96. doi: 10.1200/JCO.20.02873
22. Zamboglou C, Thomann B, Koubar K, Bronsert P, Krauss T, Rischke HC, et al. Focal Dose Escalation for Prostate Cancer Using (68)Ga-HBED-CC PSMA PET/CT and MRI: A Planning Study Based on Histology Reference. *Radiat Oncol* (2018) 13(1):81. doi: 10.1186/s13014-018-1036-8
23. Ferraro DA, Becker AS, Kranzbuhler B, Mebert I, Baltensperger A, Zeimpekis KG, et al. Diagnostic Performance of Ga-68-PSMA-11 PET/MRI-Guided Biopsy in Patients With Suspected Prostate Cancer: A Prospective Single-Center Study. *Eur J Nucl Med Mol I.* (2021) 48(10):3315–24. doi: 10.1007/s00259-021-05261-y
24. Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, Mehes G. Heterogeneity of Prostate-Specific Membrane Antigen (PSMA) Expression in Prostate Carcinoma With Distant Metastasis. *Pathol Oncol Res* (2009) 15 (2):167–72. doi: 10.1007/s12253-008-9104-2
25. Spohn SKB, Sachpazidis I, Wiehle R, Thomann B, Sigle A, Bronsert P, et al. Influence of Urethra Sparing on Tumor Control Probability and Normal Tissue Complication Probability in Focal Dose Escalated Hypofractionated Radiotherapy: A Planning Study Based on Histopathology Reference. *Front Oncol* (2021) 11:652678. doi: 10.3389/fonc.2021.652678
26. Zamboglou C, Spohn SKB, Adebahr S, Huber M, Kirste S, Sprave T, et al. PSMA-PET/MRI-Based Focal Dose Escalation in Patients With Primary Prostate Cancer Treated With Stereotactic Body Radiation Therapy (HypoFocal-SBRT): Study Protocol of a Randomized, Multicentric Phase III Trial. *Cancers (Basel)* (2021) 13(22):5795. doi: 10.3390/cancers13225795
27. Ahmed HU, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will Focal Therapy Become a Standard of Care for Men With Localized Prostate Cancer? *Nat Clin Pract Oncol* (2007) 4(11):632–42. doi: 10.1038/ncponc0959
28. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment With Curative Intent. *Eur Urol* (2017) 71 (4):618–29. doi: 10.1016/j.eururo.2016.08.003
29. Prive BM, Israel B, Schilham MGM, Muselaers CHJ, Zamecnik P, Mulders PFA, et al. Evaluating F-18-PSMA-1007-PET in Primary Prostate Cancer and Comparing it to Multi-Parametric MRI and Histopathology. *Prostate Cancer Prostatic Dis* (2021) 24(2):423–30. doi: 10.1038/s41391-020-00292-2

Conflict of Interest: CZ received funding from the German Cancer Consortium (DKTK), Naslund Medical, and the Klaus Tschira foundation, as well as honoraria from Johnson and Johnson and Novocure, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 02 November 2022
DOI 10.3389/fonc.2022.951220

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Radiation Oncology, a section of the journal Frontiers in Oncology

RECEIVED 23 May 2022
ACCEPTED 29 September 2022
PUBLISHED 02 November 2022

CITATION
Guerini AE, Noale M, Mortellaro G, Lisi R, Bruni A, Santini R, Muto P, Ferrera G, Cossali G, Morelli V, PRO-EPI study group, Magrini SM, Spiazzi L and Buglione M (2022) Early results of PRO-EPI: PROspective multicenter observational study on elective pelvic nodes irradiation in patients with intermediate/high/very high-risk non-metastatic prostate cancer submitted to radical, adjuvant, or salvage radiotherapy with or without concomitant androgen deprivation therapy.
Front. Oncol. 12:951220.
doi: 10.3389/fonc.2022.951220

Early results of PRO-EPI: PROspective multicenter observational study on elective pelvic nodes irradiation in patients with intermediate/high/very high-risk non-metastatic prostate cancer submitted to radical, adjuvant, or salvage radiotherapy with or without concomitant androgen deprivation therapy

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Simple Summary: Although radiotherapy plays a fundamental role in the management of intermediate/high/very high-risk non-metastatic prostatic cancer (IHR-nmPca), there is still no consensus on the optimal treatment strategy in this setting. Remarkably, the role of elective nodal irradiation (ENI) is still highly controversial. The PROspective multicenter observational study on Elective Pelvic nodes Irradiation (PRO-EPI) was designed to provide "real life" data regarding the patterns of care for IHR-nmPca.Forty-three Italian Radiation Oncology centers participated in the PROspective multicenter observational study on Elective Pelvic nodes Irradiation (PRO-EPI) project, with 1029 patients enrolled. In this preliminary analysis, we longitudinally evaluated the impact of

Elective Nodal Irradiation (ENI) and radiotherapy features on toxicity and quality of life (QoL). Six months follow-up data were available for 913 patients and 12 months data for 762 patients. Elective Nodal Irradiation was given to 506 patients (48.9%). Volumetric Intensity-Modulated Radiation Therapy (IMRT) was adopted in more than 77% of patients and Image-Guided Radiation Therapy (IGRT) in 84.4%. Androgen deprivation therapy (ADT) was administered to the majority of patients (68.3%), and it was associated to ENI in 408 cases (81.1%). Toxicity was mostly mild and reversible and IGRT resulted in a significant reduction of rectal toxicity, although a non-significant trend toward increased urinary toxicity was observed. No statistically significant differences in QoL and toxicity were seen in patients treated with or without ENI. The adoption of IGRT is widespread and increasing and could reduce treatment toxicity. ENI is not yet the standard treatment, but it is performed in a growing fraction of cases and not resulting into an increase in toxicity or in a deterioration of QoL. Further analyses are needed to clarify the long-term toxicity profile and the impact of ENI on survival.

KEYWORDS

prostate cancer, radiotherapy, pelvic nodal irradiation, ADT, IMRT (intensity modulated radiation therapy), IGRT (Image Guided Radiation Therapy), VMAT (volumetric modulated arc therapy)

1 Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer worldwide (1) and the first one in Italy accounting for 18.5% of the total new cancer cases in Italian male population, with an incidence rate of 2% in men aged older than 70 years (2). Prostate cancer presentation is extremely variable and this type of cancer affects a very heterogeneous group of patients, thus multiple treatment modalities can be offered.

Therefore, there are still many open questions regarding the optimal treatment of intermediate/high/very high-risk non-metastatic PCa (IHR-nmPca) patients, including the role of radiotherapy (3).

The most adequate treatment for IHR-nmPca, both for node positive and negative diseases and in primary and post-operative setting, still has to be defined. Controversial issues encompass the trade-off between the possible improvement of disease control and the risk of greater toxicities related to the addition of androgen deprivation therapy (ADT) and/or the inclusion of pelvic lymph nodes in treatment volume for radical or adjuvant radiotherapy (4–16).

Although radiotherapy plays a fundamental role in various setting of this disease, there is still no clear consensus regarding several aspects of its prescription and combination with systemic treatment (3).

Remarkably, the benefit of elective nodal irradiation (ENI) is debated, especially in node-negative disease and post-operative setting, although multiple analyses evaluated its potential impact (4, 5)

A systematic review published in 2014 by Dirix et al. (6) reported conflicting results, as whole pelvis radiotherapy (WPRT) improved disease-free survival (DFS) in retrospective trials, whereas the three randomized trials analyzed gave insufficient evidence to advocate the use of prophylactic ENI for IHR-nmPca.

In 2021, a new systematic review conducted by De Meerleer et al. (4), included RTOG 9413 (7), GETUG-01 (8), and the POP-RT trial (9). The POP-RT trial (9), in particular, showed improved DFS in a selected population of patients with a risk of nodal involvement greater than 20% in the group of prophylactic ENI as compared with prostate-only radiotherapy (PORT).

The adoption of ENI for the treatment of prostate cancer had no impact on overall survival (OS) in previous retrospective (13, 16) and prospective (11) studies. Coherently, an analysis of National Cancer Data Base of the United States did not show survival benefit from the addition of ENI for high-risk prostate cancer compared with PORT (12).

On the other hand, the lack of survival benefit could be due to the insufficient follow-up duration, and promising results were reported in term of biochemical progression-free survival (bPFS) in large retrospective studies evaluating ENI in combination with brachytherapy (13) or with ADT (16). In a prospective non-randomized trial by Tharmalingam et al. (11), ENI combined with brachytherapy resulted in a significant

improvement in 5-year bPFS in intermediate and high-risk prostate cancer compared with PORT, regardless of ADT.

The recently published SPPORT randomized phase 3 trial (17) assessed the potential benefit of adding short-term ADT only or ENI and ADT to salvage prostate bed radiotherapy: The 5-year rate of freedom from progression improved with the addition of ADT and further increased with ADT plus ENI.

Moreover, ENI generally did not increase toxicity (16) or slightly worsened acute genitourinary and gastrointestinal toxicity (11, 15, 17), and safety profile was overall fair with no difference in late toxicity (11, 16, 17) and reported quality of life (QoL) (15).

The absence of conclusive data and strong indications might lead to relevant discrepancies across different institutions and could both deprive patients from a potentially effective treatment and lead to over-treatment and unnecessary toxicities.

Therefore, we designed a large prospective multicenter study with the aim to provide updated data on the use of ENI and ADT to treat patients with PCa undergoing elective, adjuvant, or salvage radiotherapy in Italian Radiation Oncology centers.

2 Materials and methods

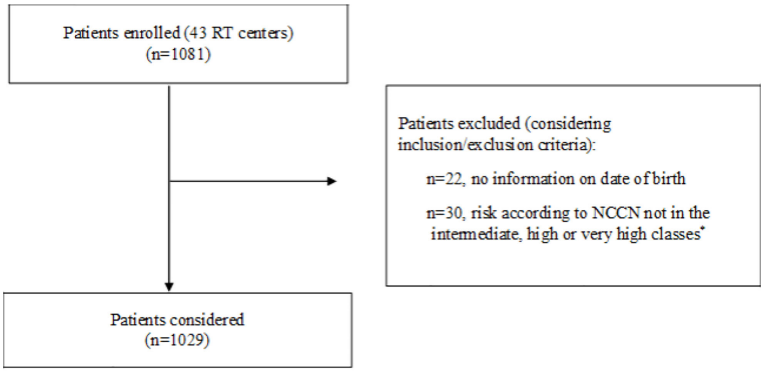
PRO-EPI is a PROspective multicenter observational study on Elective Pelvic nodes Irradiation in patients with IHR-nmPca submitted to radical, adjuvant, or salvage radiotherapy (RT) with or without concomitant ADT.

From March 2017 to March 2020, 43 radiation oncology centers located in Italy enrolled 1,081 consecutive patients that met the inclusion criteria, as shown in Figure 1. Data were collected at time of enrollment and 1, 3, 6, 12, 18, 24, 30, and 36 months later.

The study was designed and carried out in accordance with the principles of the declaration of Helsinki. The study protocol was approved by the Ethics Committee of the coordinating center and by those of the other recruiting centers. All the participants signed an informed consent form.

The primary end point was OS, whereas secondary end points were cause-specific survival (CSS), biochemical relapse-free survival (bRFS), acute and late toxicity evaluation (rectal, bladder, bowel toxicity, according to common terminology criteria for adverse events [CTCAE] version 4.0 (18) and QoL assessment according to the validated Italian version of the University of California Los Angeles-Prostate Cancer Index [UCLA-PCI] and the Short-Form Health Survey Standard v1 scale (SF-12) (19, 20).

UCLA-PCI is a questionnaire of 14 multiple choice items that evaluate urinary, rectal, and sexual bother and function: Each item can have a result between zero and 100, where zero means maximum reduction of QoL and 100 means normal QoL.



	Patients with available data	Patients deceased at each timepoint	Patients lost to follow-up at each timepoint
Baseline	1029	--	--
1-month	991	0	38
3-month	946	4	41
6-month	913	1	32
12-month	762	4	147

FIGURE 1
Flowchart of the PRO-EPI study. *Risk according to NCCN: intermediate (T2b, T2c, or Gleason score = 7 or 10 < PSA ≤ 20 ng/ml); high (T3a or Gleason score 8, 9, 10, or PSA > 20 ng/ml); very high (T3b, T4, or multiple risk factors for high risk).

SF-12 scale is a questionnaire of 12 multiple choice items that evaluate Physical Component Summary (PCS) and Mental Component Summary (MCS) through specific formulas: A higher score means better QoL.

In this preliminary analysis, the data from the first 12 months of follow-up were analyzed to evaluate the impact of ENI, ADT, and RT techniques on QoL and toxicity.

In order to compare different RT fractionations, dose to prostate and seminal vesicles was normalized to EQD2 according to this formula:

EQD2 = D (total dose given in Gy) x ([d (dose per fraction in Gy) + (α/β)]/[2 + (α/β)]).

On the basis of previous experiences (21, 22), we considered an α/β value for prostate's tumor tissue of 1.5 Gy.

2.1 Statistical analysis

The categorical variables were presented as counts and percentages, whereas the continuous were summarized using means and standard deviations (*SD*s) or median and quartiles (Q1 and Q3). Normal distributions of continuous variables were tested using the Shapiro–Wilk test. Missing values were not imputed.

Differences in baseline characteristics of participants were assessed using Fisher's exact or Chi-squared tests and Wilcoxon Rank Sum Test or generalized linear models after testing for homoschedasticity (Levene test) and for categorical and continuous variables, respectively, taking into account the following RT features: (a) aim—exclusive, adjuvant, and salvage; (b) method—image-guided radiation therapy (IGRT) *versus* no IGRT; (c) technique—three-dimensional conformal radiation therapy (3D-CRT) *versus* "step and shoot" Intensity-Modulated Radiation Therapy (IMRT) *versus* volumetric IMRT *versus* Stereotactic body radiotherapy (SBRT); (d) ENI *versus* no ENI.

Mixed-effects models were used to evaluate the changes in UCLA-PCI and SF-12 QoL scores according to ENI and RT features and time. The adjustment variables considered in the models included baseline QoL scores, age at diagnosis, comorbidities according to CIRS Comorbidity Severity Index (23, 24), presence of diabetes, and PCa risk according to NCCN. Tukey adjustments for multiple comparisons were applied.

Rectal, urinary, and bowel toxicities through follow-ups were analyzed according to RT features and ENI, considering Generalized Cochran-Mantel-Haenszel score tests of marginal homogeneity and Generalized Estimating Equations (GEEs) for ordinal repeated measures, implemented in the Genmod procedure (25) and adjusted for age at diagnosis, presence of diabetes, comorbidities according to CIRS, risk according to NCCN, and RT features.

Two-tail p-values < 0.05 were considered statistically significant. The analyses were performed using SAS statistical package, version 9.4 (SAS Institute Inc., Cary, NC, USA).

2.2 Patients and treatment characteristics

A total of 1,029 patients were enrolled; for the present analysis, 6 months follow-up data were available for 913 patients and 12 months data for 762 patients (nine died and 258 were lost to follow up, as reported in Figure 1).

Clinical target volume (CTV) included the prostate and the whole seminal vesicles, or the corresponding portions of the post-surgical bed, in 75.6% of cases treated with exclusive RT and 65.7% of patients receiving adjuvant RT.

The dose was prescribed with the objective to deliver more than 95% of the target prescription dose to at least 98% (D98% ≥ 95%) of each planning target volume (PTV) and less than 105% of prescribed doses to 2% of PTVs (D2% ≤ 105%).

Elective nodal irradiation was given to 503 patients (48.9%) and in more than 75% of cases (n = 382) the treated volumes included common iliac nodes.

3 Results

Comparing participants included in the analysis with those lost to follow up, the latter were older (70.1 ± 7.1 *vs.* 71.3 ± 7.2 years, respectively), whereas no significant differences were found in relation to clinical features.

3.1 Patients' clinical features at enrollment

Characteristics of study participants at time of enrollment are summarized in Table 1. Mean age at PCa diagnosis was 70.4 ± 7.1 years (range: 36–85). It was possible to calculate the ISUP group for all the patients: 97 (9.5%) were classified as Group 1, 235 (22.8%) as Group 2, 246 (23.9%) as Group 3, 280 (27.2%) as Group 4, and 171 (16.6%) as Group 5. The majority of patients (n = 672, 65.3%) presented high or very high NCCN risk disease, whereas the remaining 357 patients (34.7%) presented with intermediate risk disease. Median PSA at diagnosis was 10.0 ng/ml. More than 70% of patients were diagnosed with cT2 or cT3 disease according to TNM (26), whereas 10.9% of the cases had clinical positive nodes.

A comprehensive representation of patients' features, including basal urinary, bowel and sexual function or bother and Cumulative Illness Rating Scale (CIRS) is reported in Table 1. Characteristics of the study participants by treatment are described in Supplementary Tables 1 and 2 (Supplementary Material).

10.3389/fonc.2022.951220

TABLE 1 Characteristics of the study participants at the enrollment.

	***n* = 1029**
Age at diagnosis, years	
mean ± *SD*	70.4 ± 7.1
min, max	36, 85
Education, *n* (%)	
University degree or higher	142 (13.8)
High school diploma	350 (34.0)
Lower secondary school diploma	270 (26.2)
Elementary license	249 (24.2)
None	18 (1.8)
Marital status, *n* (%)	
Married or cohabiting	883 (85.9)
Widowed	55 (5.3)
Separated/divorced	56 (5.4)
Single	35 (3.4)
Diabetes mellitus, *n* (%)	248 (24.1)
CIRS-Comorbidity Index, median (Q1, Q3)	1 (0, 2)
CIRS-Severity Index, median (Q1, Q3)	1.2 (1.1, 1.5)
PSA at diagnosis, ng/ml, median (Q1, Q3)	10.0 (6.5, 16.6)
ISUP grade, *n* (%)	
1	97 (9.5)
2	235 (22.8)
3	246 (23.9)
4	280 (27.2)
5	171 (16.6)
Risk class, *n* (%)	
Intermediate	357 (34.7)
High	524 (50.9)
Very high	148 (14.4)
cT staging at diagnosis, *n* (%)	
T1	277 (26.9)
T2	414 (40.2)
T3	325 (31.6)
T4	9 (0.9)
Missing values	4 (0.4)
cN staging at diagnosis, *n* (%)	
N0	720 (70.0)
N1	112 (10.9)
NX	197 (19.1)
SF-12 PCS, mean ± SD	49.5 ± 8.0
SF-12 MCS, mean ± SD	49.9 ± 9.6
UCLA-PCI UF, mean ± SD	80.6 ± 26.9
UCLA-PCI UB, mean ± SD	75.4 ± 31.3
UCLA-PCI BF, mean ± *SD*	90.6 ± 17.0
UCLA-PCI BB, mean ± *SD*	53.0 ± 32.1
UCLA-PCI SF, mean ± *SD*	17.6 ± 27.3
UCLA-PCI SB, mean ± *SD*	87.3 ± 24.7

CIRS, Cumulative Illness Rating Scale; PSA, Prostate Specific Antigen; SD, Standard Deviation; Q1, Quartile 1; Q3, Quartile 3; UCLA-PCI, UCLA Prostate Cancer Index; UF, Urinary Function; UB, Urinary Bother; BF, Bowel Function; BB, Bowel Bother; SF, Sexual Function; SB, Sexual Bother; SF-12, Short Form survey 12; PCS, Physical Component Summary; MCS, Mental Component Summary. Scores for SF-12 PCS and MCS, and for UCLA-PCI UF, UB, BF, BB, SF, and SB range from 0 to 100, with higher scores representing better quality of life.

3.2 Treatment features

A comprehensive representation of treatment features is reported in Table 2.

The majority of patients (n = 664, 64.6%) underwent exclusive RT, whereas 30% (n = 309) received adjuvant RT and 5.4% (n = 56) salvage RT.

More than 77% (n = 800) of patients were treated with volumetric IMRT and IGRT was adopted in 84.4% (n = 868) of patients. Concomitant, adjuvant or neoadjuvant androgen deprivation therapy (ADT) was administered to most of the patients (n = 703, 68.3%) and was mainly represented by LH-RH analogues (n = 494, 70.4% of patients treated with ADT). Median duration of ADT was 15 months (Q1 9 months, Q3 18 months). The association of RT with ADT was significantly more frequent in the group of patients that underwent ENI, compared with patients that did not (81.1% *vs.* 56.1%, $p < 0.0001$).

3.3 RT dose and volumes

Mean EQD2 RT dose to prostate was significantly different depending on the aim of radiotherapy: In the group of exclusive RT 92.3% (n = 613) received a mean EQD2 to prostate ≥ 75 Gy, whereas the surgical bed received this dose only in 97 patients (31.4%) in the group of adjuvant RT and in 19 cases in the salvage RT group (33.9%).

Most of the treatments were performed with hypofractionated schedules (>2 Gy/fraction) (n = 680, 66.0%). IGRT was associated with a Hypofractionated dose fractionation schedule in 72.5% of cases (n = 629) (*vs.* no IGRT +Hypofractionated n = 36, 29.8%).

Complete RT dose and volumes features are reported in Table 3.

3.4 Elective nodal irradiation

Complete ENI features and a treatment flow diagram are reported in Table 2 and Figure 2. Median prescribed dose for ENI was 50.4 Gy and median number of fractions was 28. Dose prescription for ENI was heterogeneous: 50.4 Gy was the most commonly prescribed dose (n = 155; 30.8%) followed by 50 Gy (n = 91; 18, 1%), 45 Gy (n = 79; 15.7%), 54 Gy (n = 49; 9.7%) and 56 Gy (n = 32; 6.4%), whereas the other 19.3% had a different prescription dose. Dose per fraction was as well variable: Most patients received 1.8 Gy/fraction (n = 289; 57.5%), whereas

TABLE 2 Radiotherapy and hormone therapy features.

	n = 1029
Aim of RT, *n* (%)	
Exclusive RT	664 (64.6)
Adjuvant RT (performed within 6 months from surgery)	309 (30.0)
Salvage RT (after surgery)	56 (5.4)
RT method, *n* (%)	
IGRT	868 (84.4)
No IGRT	121 (11.7)
Missing values	40 (3.9)
RT technique, n (%)	
IMRT (step and shoot) or 3D-CRT	181 (17.5)
IMRT (volumetric)	800 (77.8)
SBRT	8 (0.8)
Not specified	40 (3.9)
Elective Nodal Irradiation, *n* (%)	
ENI	503 (48.9)
ENI including common iliac nodes	382 (75.9)
ENI not including common iliac nodes	121 (24.1)
NO ENI	526 (51.1)
ADT, *n* (%)	703 (68.3)
Type of ADT, *n* (%)	69 (9.8)
Total androgenic blockade	55 (7.8)
Androgen receptor antagonists	494 (70.4)
Luteinizing hormone-releasing hormone (LH-RH) agonists	77 (11.0)
LH-RH antagonists	1 (0.1)
Other	7 (0.9)
Not specified	
Association of RT with ADT, *n* (%)	
RT without ADT	288 (28.0)
RT + neoadjuvant ADT (before RT)	111 (10.8)
RT + adjuvant ADT (after RT)	32 (3.1)
RT + neoadjuvant + adjuvant ADT	560 (54.4)
Not specified	38 (3.7)
Association of RT with ADT, *n* (%)	
ENI group	408/503 (81.1%)
NO ENI group	295/526 (56.1%)

ADT, Androgen Deprivation Therapy; ENI, Elective Nodal Irradiation; IGRT, Image-Guided Radiation Therapy; IMRT, Intensity-Modulated Radiation Therapy; LH-RH, Luteinizing Hormone Releasing Hormone; SBRT, Stereotactic body radiotherapy; RT, Radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy.

14.9% (*n* = 75) received 2Gy/fraction, 8.5% 1.7 Gy/fraction (*n* = 43) and the remaining 19.1% a different dose per fraction.

In patients who underwent ENI, the mean dose of RT to the lymph node regions ranged from a minimum of 50.0 ± 6.9 Gy (obturator lymph nodes) to a maximum of 51.0 ± 4.4 Gy (common iliac lymph nodes). Elective nodal irradiation was performed in 100 of the 112 patients who presented with clinically positive nodes (89.3%) and 100 of the 117 patients (85.5%) with pathological positive nodes.

Androgen deprivation therapy was associated to ENI in 408 cases (81.1%). Patients treated with ENI were younger at diagnosis and had higher median PSA at diagnosis (11.5 ng/ml *vs.* 8.1 ng/ml, $p < 0.0001$). ENI was given to 405 patients with high or very high NCCN risk disease (80.5%) and 287 patients with ISUP grades 4 or 5 (57.1%).

3.5 Characteristics of the patients according to RT features

Patients treated with exclusive RT had a higher mean age at diagnosis, lower educational status, and a worse CIRS Comorbidity index compared with patients from other groups.

High and very high-risk disease (according to NCCN classification) and ISUP grade >2 were more frequent in the adjuvant RT group, whereas cT3 and cT4 disease were more commonly observed in patients treated post-operatively with both adjuvant or salvage RT.

Patients treated with exclusive RT presented also better basal mean scores of UCLA-PCI Urinary Function (UF), Urinary Bother (UB), Bowel Function (BF), Bowel Bother (BB), and Sexual Function (SF) compared with patients treated with post-surgical RT.

3.6 Quality of life

As shown in Table 4, Supplementary Tables 3A, B (Supplementary Material), QoL was assessed by UCLA-PCI and SF-12 at each time point (1, 3, 6, and 12 months). Comparing variation of UCLA-PCI and SF-12 scores over time, mixed models for repeated measures did not show statistically significant differences between patients that received ENI and patients that did not.

The lack of significant difference in QoL for ENI *versus* no ENI was maintained also taking into account separately patients that underwent prostatectomy before RT and patients that did not receive previous surgery.

Estimated mean differences and 95% CI from mixed-model repeated measures analyses, adjusted for score at diagnosis, age at diagnosis, presence of diabetes mellitus, number of comorbidities according to CIRS, risk according to NCCN, aim of the RT (exclusive, adjuvant, salvage), RT method (IGRT, no IGRT), RT technique (IMRT [step and shoot or 3D-CRT], IMRT [volumetric]), and ADT.

SF-12: data available at baseline for 1,017 patients, at month 1 for 918, at month 3 for 906, at month 6 for 857, at month 12 for 682 patients.

UCLA-PCI: data for UF available at baseline for 1,015 patients, at month 1 for 916, at month 3 for 905, at month 6 for 857, and at month 12 for 681 patients. Data for UB available at baseline for 1,010 patients, at month 1 for 917, at month 3 for 901, at month 6 for 853, and at month 12 for 678 patients. Data for BF available at baseline for 1,015 patients, at month 1 for 918, at month 3 for 904, at month 6 for 857, and at month 12 for 682 patients. Data for BB available at baseline for 990 patients, at month 1 for 896, at month 3 for 883, at month 6 for 836, and at month 12 for 661 patients.

Data for SF available at baseline for 991 patients, at month 1 for 915, at month 3 for 903, at month 6 for 854, and at month 12

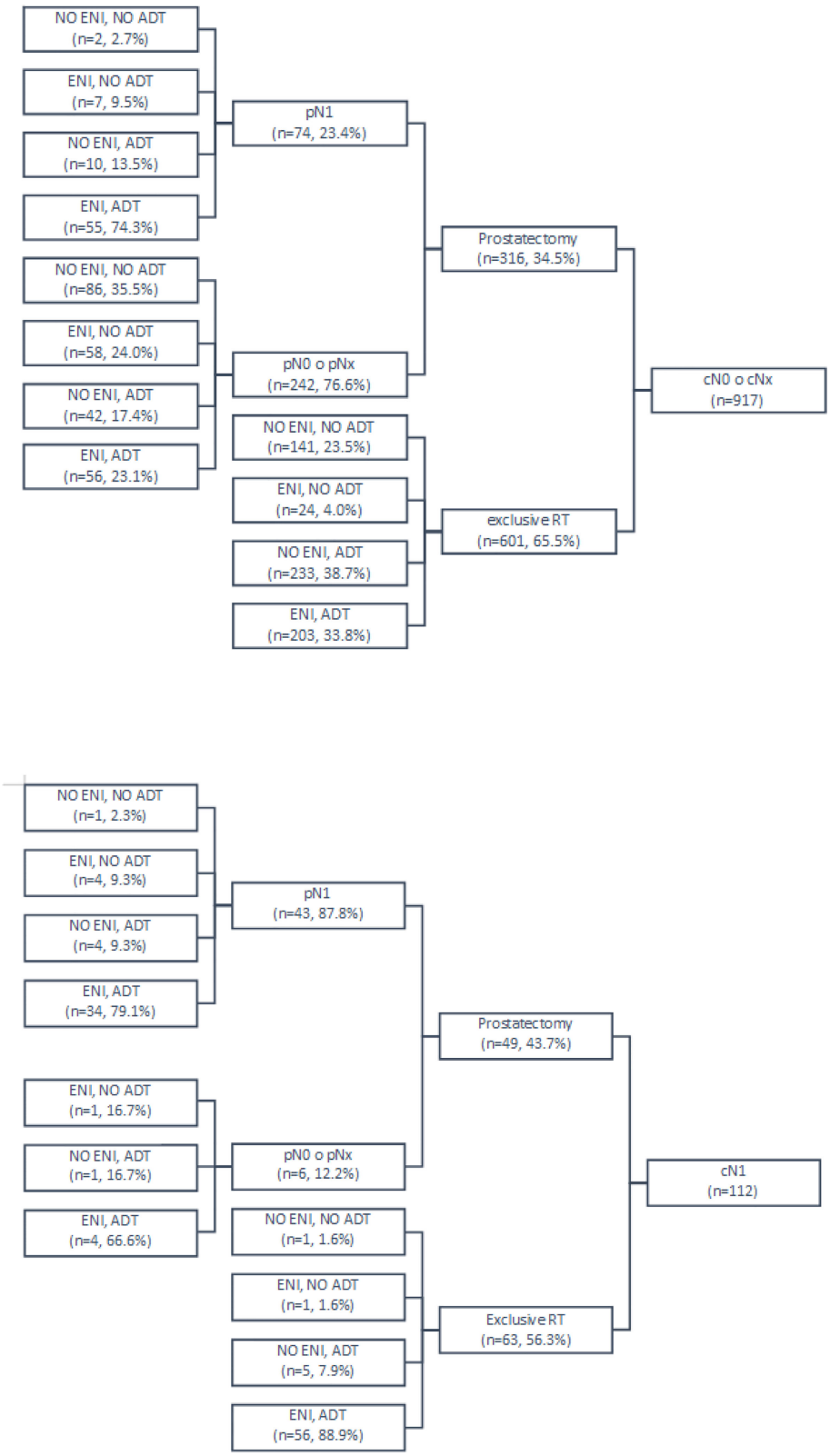


FIGURE 2
Treatment flow diagram according to nodal status.

TABLE 3 Radiotherapy dose and volumes.

	Aim of RT			*p*-value
	Exclusive RT (*n* = 664)	**Adjuvant RT (*n* = 309)**	**Salvage RT (*n* = 56)**	
Prostate *				< 0.0001 a [b]
EQD2 mean ± *SD* (Gy)	79.3 ± 5.0	72.3 ± 6.7	73.6 ± 4.0	< 0.0001
EQD2 < 70 Gy	9 (1.4)	97 (31.4)	10 (17.9)	
EQD2 70-75 Gy	42 (6.3)	115 (37.2)	27 (48.2)	
EQD2 ≥75 Gy	613 (92.3)	97 (31.4)	19 (33.9)	
Caudal portion of the seminal vesicles (CP) *				0.6359
EQD2 mean ± *SD* (Gy)	73.8 ± 8.8	72.5 ± 6.8	71.5 ± 6.8	< 0.0001
EQD2 < 70 Gy	207 (31.2)	63 (20.4)	4 (7.1)	
EQD2 70–75 Gy	45 (6.8)	78 (25.2)	7 (12.5)	
EQD2 ≥ 75 Gy	352 (53.0)	73 (23.7)	4 (7.1)	
Not included	60 (9.0)	95 (30.7)	41 (73.3)	
Seminal Vesicles (SV) *				0.0001 [a]
EQD2 mean ± *SD* (Gy)	69.2 ± 9.1	72.2 ± 7.7	68.7 ± 6.9	< 0.0001
EQD2 < 70 Gy	282 (42.4)	58 (18.8)	7 (12.5)	
EQD2 70–75 Gy	58 (8.8)	76 (24.5)	5 (8.9)	
EQD2 ≥ 75 Gy	162 (24.4)	69 (22.5)	3 (5.4)	
Not included	162 (24.4)	106 (34.2)	41 (73.2)	
CTV including				< 0.0001
Prostate only *	61 (9.2)	95 (30.7)	41 (73.2)	
Prostate + CP *	101 (15.2)	11 (3.6)	0 (0)	
Prostate + CP + SV *	502 (75.6)	203 (65.7)	15 (26.8)	

A significant difference (p < 0.05) exclusive RT versus adjuvant RT; b significant difference (p < 0.05) exclusive RT versus salvage RT; c significant difference (p < 0.05) adjuvant RT versus salvage RT; * or the corresponding portions of the post-surgical bed. CTV, clinical target volume; SD, standard deviation.

for 678 patients. Data for SB available at baseline for 1,013 patients, at month 1 for 915, at month 3 for 903, at month 6 for 854, and at month 12 for 678 patients.

3.7 Treatment toxicity

Rectal, urinary and bowel toxicity in the overall population were classified with CTCAE v.4. A graphic representation of toxicities over time is reported in Figure 3.

3.7.1 Rectal toxicity

At 12 months of follow-up, 73 cases of rectal toxicities were reported. These were classified according to CTCAE as G1 (*n* = 50, 68.5%), G2 (*n* = 19, 26.0%) and G3 (*n* = 4, 5.5%). Rectal toxicity was significantly more frequent in patients treated without IGRT compared with patients in IGRT group (14.4% *vs.* 8.9%, *p* = 0.0377); the odds ratio (OR) calculated with GEE for ordinal data was 0.58 (*p* = 0.0049, 95% confidence interval - CI [0.40, 0.85]) for IGRT. On the other hand, neither the aim of RT nor the technique nor ENI were associated with rectal toxicity (Supplementary Figure 4 and Supplementary Tables 4A, B, Supplementary Material).

3.7.2 Urinary toxicity

One hundred seventy-three cases of urinary toxicity were observed in patients with a follow-up of at least 12 months, classified as G1 (*n* = 137, 79.1%), G2 (*n* = 32, 18.5%), G3 (*n* = 2, 1.2%) and G4 (*n* = 2, 1.2%). Urinary toxicity was observed for 11.1% of patients that did not receive IGRT as opposed to 24.3% in the IGRT group (*p* = 0.0270).

The OR for urinary toxicity was of 1.41 for IGRT *versus* no IGRT (95% CI [0.98, 2.01], *p* = 0.0604). There were no statistically significant associations with ENI or RT technique, whereas previous prostatectomy correlated with urinary toxicity (OR 1.31, 95% CI 1.01–1.69, *p* = 0.0435), Supplementary Figure 5 and Supplementary Tables 5A, B (Supplementary Materials).

3.7.3 Bowel toxicity

Twenty-two cases of bowel toxicities were observed in patients followed up to at least 12 months. These were classified as G1 (*n* = 16, 72.7%) and G2 (*n* = 6, 27.3%). No cases of G3 or G4 were observed. In the group of patients not submitted to IGRT, 8.8% developed bowel toxicity versus 2.1% in the IGRT group (*p* =< 0.0001); the OR for IGRT was 0.33 (95% CI [0.19, 0.56], *p* =< 0.001).

Furthermore, bowel toxicity was more frequent in cases treated after surgery (4.8% adjuvant RT, 4.2% salvage RT) than in those submitted to exclusive RT (1.8%, *p* = 0.0310)

According to GEE for ordinal data related to bowel toxicity, there were no significant associations with the aim of RT, nor with the technique adopted, as shown in Supplementary Figure 6 and Supplementary Tables 6A, B (Supplementary Material).

TABLE 4 Comparison of variation of UCLA-PCI and SF-12 scores over time, for ENI *versus* no ENI groups (numbers indicate estimated mean difference and 95% CI).

	Estimated differences *within groups*				Estimated differences *between groups*			*p*-value interaction group*time
	ENI	***p*-value**	**No ENI**	***p*-value**		**ENI *vs.* no ENI**	***p*-value**	
UCLA-PCI UF								0.4919
					Baseline	0.53 (1.28)	0.9999	
1 month *vs.* baseline	-4.14 (0.95)	0.0004	-2.06 (0.84)	0.2121	1 month	-0.99 (1.46)	0.9976	
3 months *vs.* baseline	-3.58 (1.07)	0.0188	-2.54 (0.97)	0.1551	3 months	-0.42 (0.45)	0.9956	
6 months *vs.* baseline	-0.48 (0.79)	0.9988	-3.40 (1.07)	0.0329	6 months	-0.47 (0.46)	0.9906	
12 months *vs.* baseline	-1.33 (0.99)	0.8773	-2.59 (1.33)	0.5192	12 months	0.13 (0.50)	1.0000	
UCLA-PCI UB								0.3181
					Baseline	0.95 (1.87)	0.9996	
1 month *vs.* baseline	-9.36 (1.37)	< 0.0001	-4.56 (1.27)	0.0080	1 month	-3.14 (1.92)	0.7258	
3 months *vs.* baseline	-8.65 (1.51)	< 0.0001	-6.46 (1.41)	0.0001	3 months	-0.42 (0.45)	0.9956	
6 months *vs.* baseline	-1.90 (1.18)	0.7464	-8.25 (1.51)	< 0.0001	6 months	-0.47 (0.46)	0.9906	
12 months *vs.* baseline	-3.69 (1.36)	0.1178	-5.51 (1.85)	0.0597	12 months	0.13 (0.50)	1.0000	
UCLA-PCI BF								0.9311
					Baseline	-0.32 (1.35)	1.0000	
1 month *vs.* baseline	-5.53 (1.05)	< 0.0001	-4.73 (1.00)	< 0.0001	1 month	-1.63 (1.19)	0.8717	
3 months *vs.* baseline	-6.05 (1.09)	< 0.0001	-5.99 (1.08)	< 0.0001	3 months	-0.42 (0.45)	0.9956	
6 months *vs.* baseline	-1.26 (0.84)	0.8067	-6.17 (1.10)	< 0.0001	6 months	-0.47 (0.46)	0.9906	
12 months *vs.* baseline	-1.44 (0.95)	0.7994	-4.42 (1.26)	0.0114	12 months	0.13 (0.50)	1.0000	
UCLA-PCI BB								0.8140
					Baseline	2.66 (1.93)	0.8664	
1 month *vs.* baseline	-3.41 (1.5)	0.3142	-1.66 (1.43)	0.9412	1 month	1.27 (2.25)	0.9992	
3 months *vs.* baseline	-3.05 (1.75)	0.6600	-1.42 (1.57)	0.9852	3 months	-0.42 (0.45)	0.9956	
6 months *vs.* baseline	0.24 (1.35)	1.0000	-1.83 (1.78)	0.9703	6 months	-0.47 (0.46)	0.9906	
12 months *vs.* baseline	-0.16 (1.68)	1.0000	-4.32 (2.01)	0.3832	12 months	0.13 (0.50)	1.0000	
UCLA-PCI SF								0.1760
					Baseline	0.16 (0.06)	0.0840	
1 month *vs.* baseline	0.95 (0.05)	< 0.0001	0.22 (0.06)	0.0021	1 month	-1.42 (0.06)	< 0.0001	
3 months *vs.* baseline	-1.36 (0.07)	< 0.0001	1.14 (0.05)	< 0.0001	3 months	-0.42 (0.45)	0.9956	
6 months *vs.* baseline	0.92 (0.03)	< 0.0001	-1.24 (0.07)	< 0.0001	6 months	-0.47 (0.46)	0.9906	
12 months *vs.* baseline	-1.45 (0.05)	< 0.0001	0.06 (0.05)	0.9174	12 months	0.13 (0.50)	1.0000	
UCLA-PCI SB								0.9797
					Baseline	0.58 (1.73)	1.0000	
1 month *vs.* baseline	-6.62 (1.34)	<.0001	-4.17 (1.28)	0.0248	1 month	-1.95 (1.57)	0.9185	
3 months *vs.* baseline	-6.70 (1.41)	<.0001	-5.84 (1.38)	0.0006	3 months	-0.42 (0.45)	0.9956	
6 months *vs.* baseline	-1.67 (1.04)	0.7486	-5.97 (1.43)	0.0009	6 months	-0.47 (0.46)	0.9906	
12 months *vs.* baseline	-1.80 (1.27)	0.8484	-4.75 (1.63)	0.0697	12 months	0.13 (0.50)	1.0000	
SF-12 PCS								0.7436
					Baseline	0.27 (0.44)	0.9998	
1 month *vs.* baseline	-0.39 (0.37)	0.9680	0.01 (0.32)	1.0000	1 month	-0.40 (0.45)	0.9963	
3 months *vs.* baseline	0.10 (0.43)	1.0000	-0.15 (0.38)	0.9999	3 months	-0.42 (0.45)	0.9956	
6 months *vs.* baseline	-0.16 (0.32)	0.9997	-0.18 (0.43)	0.9999	6 months	-0.47 (0.46)	0.9906	
12 months *vs.* baseline	-0.20 (0.40)	0.9997	0.28 (0.50)	0.9993	12 months	0.13 (0.50)	1.0000	
SF-12 MCS								0.2071
					Baseline	-0.97 (0.55)	0.6543	
1 month *vs.* baseline	-0.93 (0.40)	0.2901	-0.69 (0.36)	0.5338	1 month	-0.63 (0.59)	0.9630	

(Continued)

TABLE 4 Continued

	Estimated differences *within groups*				Estimated differences *between groups*		*p*-value interaction group*time
	ENI	*p*-value	No ENI	*p*-value		ENI *vs.* no ENI	*p*-value
3 month *vs.* baseline	-0.34 (0.46)	0.9959	-0.38 (0.41)	0.9847	3 months	-0.42 (0.45)	0.9956
6 month *vs.* baseline	0.31 (0.36)	0.9902	0.29 (0.46)	0.9985	6 months	-0.47 (0.46)	0.9906
12 month *vs.* baseline	0.98 (0.43)	0.3030	0.28 (0.55)	0.9996	12 months	0.13 (0.50)	1.0000

ENI, ElectiveNodalIrradiation; UCLA-PCI, UCLA Prostate Cancer Index; UF, UrinaryFunction; UB, UrinaryBother; BF, BowelFunction; BB, BowelBother; SF, SexualFunction; SB, SexualBother; SF-12, Short Form Survey 12; PCS, Physical Component Summary; MCS, Mental Component Summary.

There was as well no statistically significant association between ENI and intestinal toxicity (OR 1.20, 95% CI [0.73–1.97], $p = 0.4767$).

4 Discussion

Up to date, there is a lack of solid data allowing to strongly recommend precautional pelvic nodal irradiation, especially in patients without clinical lymph node involvement at diagnosis (4, 5). The PRO-EPI study was designed to prospectively evaluate the current role of ENI for the treatment of patients with IHR-nmPca in a "real world" setting.

While the follow-up is still too short to draw conclusions regarding OS, CSS, and BRFS, in this preliminary analysis, we evaluated the impact of ENI, ADT, and RT techniques on QoL and toxicity.

Moreover, this large sample of patients provided a comprehensive insight into the treatment paths that are at present endorsed by multiple Italian institutions (43 centers involved), and it is hence representative of the current Italian scenario.

The first relevant data concern the growing use of IGRT and volumetric IMRT, which have been adopted in about 85 and 75% of the cases, respectively.

This finding confirms the striking and relentless evolution of RT techniques, if we consider that in the recently published POP III study, which analyzed the pattern of practice of Italian radiation oncology centers in 2004–2011 period, IGRT was used only in 13% of cases (27).

The use of ENI as well apparently increased over time; as in POP III study, it was prescribed only to 4% of cases (27), whereas in this analysis about half of the patients received prophylactic pelvic irradiation. On the other hand, this demonstrates that there is still no consensus regarding the opportunity to offer ENI to IHR-nmPca patients. From the data collected, it is also possible to deduce that Italian radiation oncologists propose ENI more often to patients with negative prognostic factors, such as a higher ISUP score, a higher clinical T or higher initial PSA level. This is in line with the recommendations derived from the recently published POP-RT study (8).

The characteristics of patients undergoing exclusive radiotherapy are similar to those already described in previous studies, such as Pros-IT (28): older, with more comorbidities and a lower level of education than patients who have previously undergone surgery.

As expected, patients undergoing adjuvant RT tended to have a higher NCCN risk class and cT3 or cT4 diseases are more represented among patients treated post-operatively.

Regarding the QoL perceived by patients, the SF-12 and UCLA questionnaires revealed that there were no significant differences in the trajectories of QoL domains up to 12 months after treatment between patients who underwent ENI and patients that did not. Of note, we reported no statistically significant difference in QoL measures between patients that received ENI *versus* patients that did not, despite ADT was administered in a larger fraction of subjects in ENI group (81.1% *vs.* 56.1%). This result was coherent with the absence of an increase in rectal, urinary, and bowel toxicity reported by the clinicians. It has to be noted that, while a larger decrease in QoL could be expected due to the concurrent use of ADT, some previous experience retrieved a limited impact of its administration on global QoL in patients with prostate cancer. For example, the CaPSURE registry enrolled 3,068 men, comparing QoL of patients that underwent prostatectomy, RT with or without ADT and ADT alone: Treatment group was not associated in clinically meaningful decrease in QoL (29). Patient-reported outcome measures (PROMs) and QoL assessment are a valuable mean to improve the communication between clinicians and patients, detect side effects and optimize therapeutic workflow and supportive care (30). Nonetheless, although questionnaires such as SF-12 have been validated for cancer patients, the self-reported nature of the data might be flawed by recall bias, remarkably for intimate topics such as sexual function (31).

Statistically significant differences were seen in QoL at the time of recruitment between patients who had previously undergone surgery and those who were candidates for exclusive RT treatment, as already reported in previous experiences (32).

Patients undergoing radical RT, compared with those previously treated with surgery, tended to have better basal

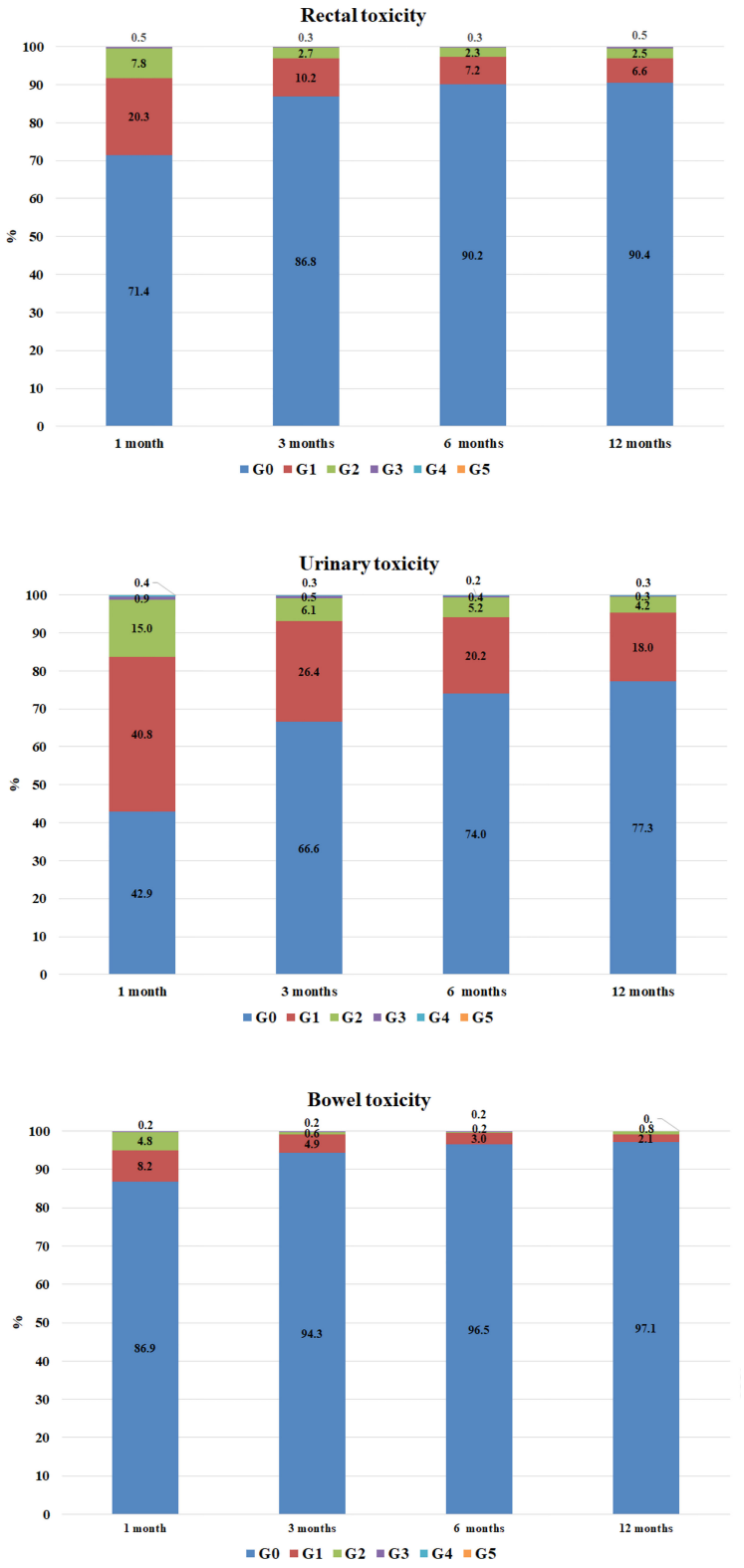


FIGURE 3
Rectal and urinary and bowel toxicity in the overall population, by time. Rectal toxicities: data available at 1 month for 990 patients, at 3 months for 965, at 6 months for 925, at 12 months for 762 patients. Urinary toxicities: data available at 1 month for 990 patients, at 3 months for 965, at 6 months for 926, and at 12 months for 762 patients.

scores on the questionnaires administered at the time of recruitment.

The toxicity profile was overall fair, as rates of G3–G4 adverse events were extremely low. The trend, as shown in Figure 3, is characterized by a higher frequency of mild and mostly urinary acute toxicity and by a subsequent progressive and gradual reduction in the severity and frequency of the side effects.

Remarkably, the group of subjects treated with ENI did not report higher rates and/or severity of adverse events compared with patients that received RT only to the prostate and seminal vesicles. In previous experiences, ENI toxicity profile was as well overall safe: While in some instances it slightly increased acute toxicity (11, 15, 17), it did not increase late toxicity (11, 16). In the SPPORT randomized phase 3 trial, adding ENI to prostate-bed RT in the salvage setting resulted in a greater rate of acute grade 2 or worse adverse events, but no significant difference was reported for late toxicity apart from increased hematologic side effects (17). Although final conclusions still could not be drawn regarding the indication of ENI, this lack of increased toxicity combined with the potential benefit in term of disease control could support its use at least in patients with clinically positive lymph nodes or at higher risk of nodal relapse. For example, in the salvage setting after surgery, addition of ENI to ADT and radiotherapy on the prostate bed resulted in higher rates of freedom from disease progression at 5 years in the phase 3 randomized SPPORT trial (17).

The adoption of IGRT resulted in a significant reduction of rectal and intestinal toxicity. On the other hand, a non-statistically significant trend toward higher urinary toxicity was reported in IGRT group. This finding could be explained by the greater use of hypofractionated RT schedule in these patients. A similar trend, with a mild statistically significant increase in late urinary toxicity in patients undergoing hypofractionated IGRT, compared with the no IGRT group, was also found in a recent study by Jereczek et al. (33).

The limits of this study must be as well acknowledged. First, this represents only a preliminary analysis, as long-term data are awaited to define the impact of different treatment modalities and techniques on clinical outcomes and late toxicities [including, e.g., the metabolic effects of ADT (34)].

The other main limit is the high rate of patients lost to follow up at 12 months (25%). In order to provide a comprehensive picture of the adoption of ENI and ADT in Italian radiation oncology centers, 43 institutions were enrolled. Unfortunately, compliance of some participants to timely transmit collected data for this preliminary analysis was sub-optimal. This highlighted the necessity of a coordinated and continuous data monitoring, given the high number of involved institutions. Dedicated measures have been taken to overcome this pitfall and reduce the number of patients lost at follow-up in the final analysis of the study.

Defining a correlation between dosimetric parameters and clinical outcomes is essential to evaluate the actual benefit of modern radiotherapy techniques such as IMRT and IGRT. In this preliminary study, information regarding the ionizing radiation dose received by the OARs was not evaluated, but we are currently collecting data to integrate a dosimetric analysis in the final results of the study. These data should be as well interpreted according to the results of multiple recent trials, suggesting that α/β ratio for prostate cancer could be higher than previously estimated (35).

Moreover, since the start of this study, modern imaging and radiotherapy techniques that can change IHR-nmPca treatment have been increasingly adopted.

Next generation imaging (including whole-body diffusion-weighted MRI and positron emission tomography), with novel radiopharmaceuticals, is increasingly used as a mean to allow optimal local staging and early identification of distant metastases (36).

Remarkably, the adoption of prostate-specific membrane antigen PET/CT (PSMA-PET/CT) is rapidly expanding due to its ability to detect nodal disease earlier than conventional imaging and at relatively lower levels of PSA (36, 37).

The recently published results of the prospective, randomized proPSMA trial (33) confirmed that PSMA-PET/CT has higher sensitivity and specificity compared with conventional imaging (CT and bone scan) both for nodal and distant metastasis in men with high-risk prostate cancer undergoing staging before curative-intent therapy.

Although, currently, PSMA-PET/CT is mostly used for re-staging the disease after biochemical recurrence (37, 38), its integration in frontline staging at first diagnosis for IHR-nmPca could provide information not detectable with conventional imaging in a large fraction of patients, which might change the management in about a third of the cases (39).

The widespread use of PSMA-PET/CT in this setting could thus improve the diagnostic process and allow to offer a more tailored treatment, for example, allowing an early identification of low-burden node positive patients that could benefit from ENI.

Emerging RT techniques, such as MR-guided radiotherapy, could further change the landscape of IHR-nmPca treatment and preliminary studies suggest promising results in term of tolerability and dosimetric results (40).

Nonetheless, it should be considered that the potential clinical benefit of these innovative imaging and radiotherapy options still has to be assessed and clarified.

5 Conclusions

This preliminary analysis highlighted the widespread and growing use of IGRT and volumetric IMRT in Italy for the

treatment of IHR-nmPca, potentially allowing a further reduction of RT-induced toxicity.

Although there is currently no consensus regarding the indications for ENI for IHR-nmPca, its adoption seemed to increase over years as well.

In our series, offering ENI to intermediate and high-risk patients did not translate into an increase in short-term toxicity or in a deterioration of quality of life, the main concerns limiting its use. Follow-up of our series is too short to draw significant conclusions regarding the impact of different techniques, ENI and ADT on disease control and survival.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by Spedali Civili di Brescia Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

PRO-EPI study group

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Funding

This research received non conditioning funding from Takeda

Acknowledgments

We would like to thank Dr. Filippo Bertoni for his contribution as an advisor to the Principal Investigator and for the coordination of the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.951220/full#supplementary-material

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* (2021) 71(3):209–49. doi: 10.3322/caac.21660

2. I NUMERI DEL CANCRO IN ITALIA 2020, in: *Associazione italiana registri tumori*. Available at: https://www.aiom.it/wp-content/uploads/2020/10/2020_Numeri_Cancro-operatori_web.pdf (Accessed Oct 11, 2021).

3. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol* (2021) 79(2):243–62. doi: 10.1016/j.eururo.2020.09.042

4. De Meerleer G, Berghen C, Briganti A, Vulsteke C, Murray J, Joniau S, et al. Elective nodal radiotherapy in prostate cancer. *Lancet Oncol* (2021) 22(8):e348–57. doi: 10.1016/S1470-2045(21)00242-4

5. Francolini G, Stocchi G, Detti B, Di Cataldo V, Bruni A, Triggiani L, et al. Dose-escalated pelvic radiotherapy for prostate cancer in definitive or postoperative setting. *Radiol Med* (2022) 127(2):206–13. doi: 10.1007/s11547-021-01435-8

6. Dirix P, Joniau S, Van den Bergh L, Isebaert S, Oyen R, Deroose CM, et al. The role of elective pelvic radiotherapy in clinically node-negative prostate cancer: A systematic review. *Radiotherapy Oncol* (2014) 110(1):45–54. doi: 10.1016/J.RADONC.2013.06.046

7. Roach M, Moughan J, Lawton CAF, Dicker AP, Zeitzer KL, Gore EM, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. *Lancet Oncol* (2018) 19(11):1504–15. doi: 10.1016/S1470-2045(18)30528-X

8. Pommier P, Chabaud S, Lagrange JL, Richaud P, Le Prise E, Wagner JP, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? update of the long-term survival results of the GETUG-01 randomized study. *Int J Radiat Oncology Biology Phys* (2016) 96(4):759–69. doi: 10.1016/J.IJROBP.2016.06.2455

9. Murthy V, Maitre P, Kannan S, Panigrahi G, Krishnatry R, Bakshi G, et al. Prostate-only versus whole-pelvic radiation therapy in high-risk and very high-risk prostate cancer (POP-RT): Outcomes from phase III randomized controlled trial. *J Clin Oncol* (2021) 39(11):1234–42. doi: 10.1200/JCO.20.03282

10. Mendez LC, Arifin AJ, Bauman GS, Velker VM, Ahmad B, Lock M, et al. Is hypofractionated whole pelvis radiotherapy (WPRT) as well tolerated as conventionally fractionated WPRT in prostate cancer patients? the HOPE trial. *BMC Cancer* (2020) 20(1):1–9. doi: 10.1186/S12885-020-07490-0

11. Tharmalingam H, Tsang Y, Choudhury A, Alonzi R, Wylie J, Ahmed I, et al. External beam radiation therapy (EBRT) and high-Dose-Rate (HDR) brachytherapy for intermediate and high-risk prostate cancer: The impact of EBRT volume. *Int J Radiat Oncol Biol Phys* (2020) 106(3):525–33. doi: 10.1016/J.IJROBP.2019.09.044

12. Amini A, Jones BL, Yeh N, Rusthoven CG, Armstrong H, Kavanagh BD. Survival outcomes of whole-pelvic versus prostate-only radiation therapy for high-risk prostate cancer patients with use of the national cancer data base. *Int J Radiat Oncol Biol Phys* (2015) 93(5):1052–63. doi: 10.1016/j.ijrobp.2015.09.006

13. Sandler KA, Cook RR, Ciezki JP, Ross AE, Pomerantz MM, Nguyen PL, et al. Prostate-only versus whole-pelvis radiation with or without a brachytherapy boost for Gleason grade group 5 prostate cancer: A retrospective analysis. *Eur Urol* (2020) 77(1):3–10. doi: 10.1016/j.eururo.2019.03.022

14. Dearnaley D, Griffin CL, Lewis R, Mayles P, Mayles H, Naismith OF, et al. Toxicity and patient-reported outcomes of a phase 2 randomized trial of prostate and pelvic lymph node versus prostate only radiotherapy in advanced localised prostate cancer (PIVOTAL). *Int J Radiat Oncol Biol Phys* (2019) 103(3):605–17. doi: 10.1016/j.ijrobp.2018.10.003

15. Murthy V, Maitre P, Bhatia J, Kannan S, Krishnatry R, Prakash GJ, et al. Late toxicity and quality of life with prostate only or whole pelvic radiation therapy in high risk prostate cancer (POP-RT): A randomised trial. *Radiother Oncol* (2020) 145:71–80. doi: 10.1016/j.radonc.2019.12.006

16. Mantini G, Tagliaferri L, Mattiucci GC, Balducci M, Frascino V, Dinapoli N, et al. Effect of whole pelvic radiotherapy for patients with locally advanced prostate cancer treated with radiotherapy and long-term androgen deprivation therapy. *Int J Radiat Oncol Biol Phys* (2011) 81(5):e721–6. doi: 10.1016/j.ijrobp.2010.12.003

17. Pollack A, Karrison TG, Balogh AG, Gomella LG, Low DA, Bruner DW, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. *Lancet* (2022) 399(10338):1886–901. doi: 10.1016/S0140-6736(21)01790-6

18. *Common terminology criteria for adverse events (CTCAE) version 4.0* (2009). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm (accessed September 1, 2022).

19. Gacci M, Livi L, Paiar F, Detti B, Litwin MS, Bartoletti R, et al. Quality of life after radical treatment of prostate cancer: Validation of the Italian version of the university of California-Los Angeles prostate cancer index. *Urology* (2005) 66(2):338–43. doi: 10.1016/j.urology.2005.02.027

20. Ware J Jr, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* (1996) 34(3):220–33. doi: 10.1097/00005650-199603000-00003

21. Fowler JF, Ritter MA, Chappell RJ, Brenner DJ. What hypofractionated protocols should be tested for prostate cancer? *Int J Radiat. Oncol Biol Phys* (2003) 56:1093–104.

22. Ritter M. Rationale, conduct, and outcome using hypofractionated radiotherapy in prostate cancer. *Semin Radiat Oncol* (2008) 18:249–56. doi: 10.1016/j.semradonc.2008.04.007

23. Conwell Y, Forbes NT, Cox C, Caine ED. Validation of a measure of physical illness burden at autopsy: the cumulative illness rating scale. *J Am Geriatr Soc* (1993) 41(1):38–41. doi: 10.1111/j.1532-5415.1993.tb05945.x

24. Corrao S, Natoli G, Nobili A, Manucci PM, Pietrangelo A, Perticone F, et al. Comorbidity does not mean clinical complexity: evidence from the RePoSI register. *Intern Emerg Med* (2020) 15(4):621–8. doi: 10.1007/s11739-019-02211-3

25. Yang B. *Analyzing ordinal repeated measures data using SAS®*. Bonita Springs, FL, USA: PharmaSUG Proceedings: Statistics and Pharmacokinetics (2006).

26. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours. 8th ed*. Chichester, UK; Hoboken, NJ, USA: John Wiley & Sons, Inc (2017).

27. Mazzeo E, Triggiani L, Frassinelli L, Guarneri A, Bartoncini S, Antognoni P, et al. How has prostate cancer radiotherapy changed in Italy between 2004 and 2011? an analysis of the national patterns-Of-Practice (POP) database by the uro-oncology study group of the Italian society of radiotherapy and clinical oncology (AIRO). *Cancers (Basel)* (2021) 13(11):2702. doi: 10.3390/cancers13112702

28. Buglione M, Noale M, Bruni A, Antonelli A, Bertoni F, Corvo' R, et al. Treatment paths for localised prostate cancer in Italy: The results of a multidisciplinary, observational, prospective study (Pros-IT CNR). *PloS One* (2019) 14(11):e0224151. doi: 10.1371/journal.pone.0224151

29. Cary KC, Singla N, Cowan JE, Carroll PR, Cooperberg MR. Impact of androgen deprivation therapy on mental and emotional well-being in men with prostate cancer: analysis from the CaPSURE™ registry. *J Urol* (2014) 191(4):964–70. doi: 10.1016/j.juro.2013.10.098

30. Di Maio M, Basch E, Denis F, Fallowfield LJ, Ganz PA, Howell D, et al. The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO clinical practice guideline. *Ann Oncol* (2022) 33(9):878–92. doi: 10.1016/j.annonc.2022.04.007

31. Bhandari NR, Kathe N, Hayes C, Payakachat N. Reliability and validity of SF-12v2 among adults with self-reported cancer. *Res Soc Adm Pharm* (2018) 14(11):1080–4. doi: 10.1016/j.sapharm.2018.01.007

32. Noale M, Bruni A, Triggiani L, Buglione M, Bertoni F, Frassinelli L, et al. Impact of gastrointestinal side effects on patients' reported quality of life trajectories after radiotherapy for prostate cancer: Data from the prospective, observational pros-IT CNR study. *Cancers (Basel)* (2021) 13(6):1479. doi: 10.3390/cancers13061479

33. Jereczek-Fossa BA, Surgo A, Maisonneuve P, Maucieri A, Gerardi MA, Zerini D, et al. Late toxicity of image-guided hypofractionated radiotherapy for prostate: non-randomized comparison with conventional fractionation. *Radiol Med* (2019) 124(1):65–78. doi: 10.1007/s11547-018-0937-9

34. Palumbo C, Antonelli A, Triggiani L, Dalla Volta A, Maffezzoni F, Zamboni S, et al. Changes in body composition and lipid profile in prostate cancer patients without bone metastases given degarelix treatment: the BLADE prospective cohort study. *Prostate Cancer Prostatic Dis* (2021) 24(3):852–9. doi: 10.1038/s41391-021-00345-0

35. Datta NR, Stutz E, Rogers S, Bodis S. Clinical estimation of α/β values for prostate cancer from isoeffective phase III randomized trials with moderately hypofractionated radiotherapy. *Acta Oncol* (2018) 57(7):883–94. doi: 10.1080/0284186X.2018.1433874

36. Perez-Lopez R, Tunariu N, Padhani AR, Oyen WJG, Fanti S, Vargas HA, et al. Imaging diagnosis and follow-up of advanced prostate cancer: Clinical perspectives and state of the art. *Radiology* (2019) 292(2):273–86. doi: 10.1148/radiol.2019181931

37. Papa N, Perera M, Murphy DG, Lawrentschuk N, Evans M, Millar JL, et al. Patterns of primary staging for newly diagnosed prostate cancer in the era of prostate specific membrane antigen positron emission tomography: A population-based analysis. *J Med Imaging RadiatOncol* (2021) 65(6):649–54. doi: 10.1111/1754-9485.13162

38. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet* (2020) 395(10231):1208–16. doi: 10.1016/S0140-6736(20)30314-7

39. Ferraro DA, Garcia Schüler HI, Muehlematter UJ, Eberli D, Müller J, Müller A, et al. Impact of 68Ga-PSMA-11 PET staging on clinical decision-making in patients with intermediate or high-risk prostate cancer. *Eur J Nucl Med Mol Imaging* (2020) 47(3):652–64. doi: 10.1007/s00259-019-04568-1

40. Cuccia F, Corradini S, Mazzola R, Spiazzi L, Rigo M, Bonù ML, et al. MR-guided hypofractionated radiotherapy: Current emerging data and promising perspectives for localized prostate cancer. *Cancers (Basel)* (2021) 13(8):1791. doi: 10.3390/cancers13081791

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