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Local Radiotherapy and Androgen Deprivation Therapy (ADT) Monotherapy for Low-Volume Metastatic Hormone-Sensitive Prostate Cancer: Real-World Outcomes in the Era of PSMA PET-CT Staging

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Abstract

Background

Randomized trials established the survival benefit of primary tumor radiotherapy (RT) in low-volume metastatic hormone-sensitive prostate cancer (mHSPC), typically alongside upfront docetaxel or androgen receptor pathway inhibitors (ARPI). However, in real-world practice, systemic intensification is frequently omitted due to age, comorbidities, or cost. In parallel, diagnostic imaging has shifted from conventional CT and bone scan to PSMA PET-CT. We hypothesized that patients with low metastatic burden accurately staged via highly sensitive PSMA PET-CT can achieve durable survival with prostate RT and androgen deprivation therapy (ADT) alone.

Methods

We retrospectively reviewed patients with newly diagnosed, PSMA PET-CT-staged, low-volume mHSPC treated at a single center between January 2019 and April 2025. All received high-dose prostate RT and continuous ADT monotherapy. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Univariate and multivariate Cox regression models were utilized to identify prognostic factors for PFS.

Results

Fifty patients were identified. The most common radiotherapy fractionation was 55 Gy in 20 fractions (n=45, 90%). At a median follow-up duration of 31 months, median PFS and OS were not reached. The two-year OS and PFS were 96% and 82%, respectively. On univariate analysis, favorable prognostic factors included non-T4 stage, low PSA at six months post-RT, PSA <0.2 ng/mL at six months post-RT, and low absolute PSA nadir. PSA <0.2 ng/mL at six months post-RT remained as a significant prognostic factor in multivariate analysis. The two-year PFS for patients achieving a PSA <0.2 ng/mL at six months was higher than those with PSA ⩾ 0.2 ng/mL (96% vs. 61%, HR 0.07, 95% CI 0.01-0.57, p=0.013).

Conclusion

While upfront systemic treatment intensification remains the current standard of care for mHSPC, for patients with low-volume disease staged by PSMA PET-CT who cannot receive or tolerate upfront systemic intensification, preliminary data show pairing prostate RT with ADT monotherapy still achieves favorable PFS and OS, and is an explorable alternative that should be validated by prospective studies. A six-month post-RT PSA threshold of <0.2 ng/mL is a significant prognostic factor for PFS and could be explored for its utility in identifying candidates for continued de-escalated therapy versus those requiring timely systemic re-intensification.

Categories: Urology, Radiation Oncology, Oncology
Keywords: androgen deprivation therapy (adt), hormone-sensitive prostate cancer, oligometastasis, prostate cancer, radiotherapy (rt)

Introduction

The therapeutic landscape for upfront metastatic hormone-sensitive prostate cancer (mHSPC) has evolved from androgen-deprivation therapy (ADT) monotherapy to intensive combinations incorporating docetaxel and/or androgen receptor pathway inhibitors (ARPIs) [1-5]. For low-volume disease - defined by the CHAARTED criteria as four or fewer bone metastases confined to the axial skeleton without visceral involvement - prostate radiotherapy resulted in an overall survival (OS) benefit of 7% at three years in the STAMPEDE trial [6,7]. Conversely, the PEACE-1 trial demonstrated a progression-free survival (PFS) benefit

of local radiotherapy with the addition of abiraterone to the standard of care (SOC) in low-volume mHSPC, but no survival advantage was observed with local radiotherapy within the SOC-alone cohort or across the broader low-volume population [8]. Because both trials permitted or mandated upfront docetaxel as part of the SOC (18% in STAMPEDE and 50% in PEACE-1), the definitive benefit of prostate radiotherapy, particularly alongside intensified systemic therapies, remains contentious.

In real-world clinical practice, management frequently diverges from clinical trial protocols. Intensified upfront regimens utilizing docetaxel or ARPIs are often deferred or omitted due to advanced age, comorbidities, or financial constraints; for example, a US SEER database study reported that 47% of older patients received ADT alone, compared to 15% for ADT plus ARPI and 6% for ADT plus docetaxel [9]. Furthermore, staging modalities have shifted from conventional CT and technetium bone scans - the standards in STAMPEDE and PEACE-1 - to 68Ga/18F-prostate-specific membrane antigen (PSMA) PET-CT due to its superior sensitivity and specificity [10]. Highly sensitive PSMA PET-CT staging minimizes understaging, ensuring that patients classified as low-volume do not harbor occult, high-volume metastasis.

We hypothesized that in patients with truly low disease burden as staged by PSMA PET-CT, prostate radiotherapy still retains its benefit without intensification of systemic treatment. This study evaluated outcomes and prognostic factors in patients with low-volume mHSPC staged by PSMA PET-CT who received prostate radiotherapy and ADT monotherapy, aiming to explore potential treatment de-escalation pathways and inform strategies for subsequent systemic re-intensification.

Materials And Methods

This retrospective cohort study evaluated patients with de novo, low-volume mHSPC (per CHAARTED criteria) who underwent prostate radiotherapy at Queen Elizabeth Hospital, Hong Kong, between January 2019 and April 2025. Patient demographics, disease characteristics, clinician assessments, diagnostic results, and radiotherapy plans were extracted from the Electronic Patient Record system. All patients underwent a baseline PSMA PET-CT prior to initiation of radiotherapy and were restaged according to the 8th edition of the American Joint Committee on Cancer TNM classification [11].

External beam radiotherapy was delivered at a dose of 55 Gy in 20 fractions, or an equivalent or higher biologically effective dose (EQD2) by intensity-modulated radiotherapy or volumetric modulated arc therapy. RT was planned with CT simulation and given to patients in supine with an empty rectum and full bladder. The planning target volume (PTV) included the prostate only with an 8 mm posterior margin and 10mm margin elsewhere for patients who received 55Gy/20Fr, while PTV is variable according to local protocol for other fractionations and when pelvic nodal irradiation was incorporated. Concurrent radiation to pelvic lymph nodes or bone metastases - either integrated into the prostate field, delivered via stereotactic body radiotherapy (SBRT), or via conventional palliative regimens - was permitted. All patients received continuous ADT monotherapy via bilateral orchidectomy or a luteinizing hormone-releasing hormone agonist/antagonist (LHRHa). Concurrent bicalutamide was permitted for a maximum of four weeks at LHRHa initiation. Patients receiving upfront docetaxel or ARPIs were excluded.

Baseline performance status was graded using the Eastern Cooperative Oncology Group (ECOG) scale during the final clinical consultation prior to radiotherapy [12]. PFS was measured from the first day of radiotherapy to the date of disease progression, death, or censoring, while OS was measured from the first day of radiotherapy to the date of death from any cause, or censoring at last documented contact. Disease progression was defined as either a rise in serum prostate-specific antigen (PSA) ⩾2.0 ng/mL from nadir confirmed by at least two consecutive rises, or radiographic progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [13]. Post-radiotherapy follow-up included PSA monitoring every three to six months initially, transitioning to a variable schedule based on biochemical stability. Treatment-related toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [14].

Primary endpoints included PFS and OS, which were estimated using the Kaplan-Meier method. Median follow-up was calculated by the reverse Kaplan-Meier method. Secondary endpoints investigated the impact on PFS of prognostic factors including TNM stage, Gleason score [15,16], number of bone metastases, baseline PSA, and six-month post-radiotherapy PSA nadir, which were evaluated with log-rank tests and Cox regression. Statistically significant univariate predictors ($p<0.05$) were subsequently evaluated via an exploratory multivariate Cox regression model to identify independent prognostic factors.

Results

Patient characteristics

A total of 50 patients were included. The median age was 72 years, and 94% had an ECOG performance status of 0 or 1. Histological confirmation of adenocarcinoma was available for 44 patients (88%), with the acinar subtype explicitly documented in 29 cases. Histopathology records could not be retrieved for two patients biopsied externally, and four patients were diagnosed clinically based on classic imaging features and elevated PSA values (22.6 - 391 ng/mL). The majority of patients presented with high-risk, locally advanced disease: 58% had Gleason grade group 4 or 5, 62% had ⩾T3 disease, and 56% had N1 disease.

Notably, 38% of the cohort presented with isolated distant nodal metastases without skeletal involvement (M1a). Among the 30 patients with bone metastases, a solitary metastasis was most common (57%), followed by two (27%) and three (17%) metastases.

Most patients received prostate radiotherapy at a dose of 55 Gy in 20 fractions (90%); four patients received 72 Gy in 36 fractions, and one received 57.5 Gy in 23 fractions. Pelvic lymph node irradiation was administered to four patients (8%). All patients completed their scheduled radiotherapy, with 28 (56%) and eight (16%) patients experiencing grade 1 and 2 gastrointestinal and/or genitourinary toxicities, respectively; one patient had grade 3 gastrointestinal toxicity with rectal bleeding, and no patient had grade 4 toxicity or above. Although radiotherapy to bone metastases was permitted, only five patients (10%) received high-dose radiation to osseous lesions concurrently via the prostate field (two received 55Gy/20Fr and one received 66Gy/36Fr) or separately via SBRT (35Gy/5Fr and 27Gy/3Fr respectively); three patients received palliative bone radiotherapy (20Gy/5Fr). Baseline characteristics are detailed in Table *1*.

Patient demographics	
Age, y (range)	72 (51-82)
≤60	5 (10%)
61-70	17 (34%)
70-80	25 (50%)
>80	3 (6%)
ECOG performance status	
0	7 (14%)
1	40 (80%)
2	3 (6%)
Smoking status	
Smoker / ex-smoker	25 (50%)
Non-smoker	25 (50%)
Disease characteristics histology	
Adenocarcinoma	44 (88%)
Acinar	29 (58%)
Subtype not specified	15 (30%)
Unknown	2 (4%)
Biopsy not performed	4 (8%)
Gleason score	
3+3	4 (8%)
3+4	2 (4%)
4+3	9 (18%)
4+4 or 3+5 or 5+3	7 (14%)
5+4 or 4+5 or 5+5	22 (44%)
Unknown	6 (12%)
T stage	
T1 or T2	19 (38%)
T3a	8 (16%)
T3b	15 (30%)
T4	8 (16%)

N stage	
N0	22 (44%)
N1	28 (56%)
M stage	
M1a	19 (38%)
M1b	31 (62%)
Number of bone metastasis	
0	19 (38%)
1	17 (34%)
2	8 (16%)
3	5 (10%)
4	1 (2%)
Radiotherapy dose to prostate	
55Gy/20Fr	45 (90%)
72Gy/36Fr	4 (8%)
57.5Gy/23Fr	1 (2%)
Radiotherapy to pelvic lymph node	
Yes	4 (8%)
No	46 (92%)
Radiotherapy to bone metastasis	
Yes	9 (18%)
Inside local pelvic RT field	3 (6%)
SBRT	2 (4%)
Palliative RT	4 (8%)
No	41 (82%)
Baseline PSA (ng/mL)	58 (5.9 – 955)
PSA 6 months after radiotherapy (ng/mL)	0.1 (0 – 21.6)
PSA nadir (ng/mL)	0 (0 – 10.3)

TABLE 1: Baseline characteristics (n=50)*

ECOG = Eastern Cooperative Oncology Group; Fr = Fraction; Gy = Gray; PSA = Prostate specific antigen; RT = Radiotherapy; SBRT = stereotactic body radiotherapy; TNM stage = tumor, node, metastasis stage

* Data are shown as No. (%) or median (range)

Efficacy outcomes

At a median follow-up of 31 months, neither the median OS nor median PFS had been reached; 11 progressions and 3 deaths were recorded at data cut-off. The two-year OS and PFS rates were 96% and 82%, respectively (Figures *1*, *2*). Despite a wide baseline PSA range (median: 58 ng/mL; range: 5.9-955 ng/mL), the median PSA declined to 0.1 ng/mL at six months post-radiotherapy, with 27 patients (54%) achieving a PSA <0.2 ng/mL. Thirty patients (60%) achieved a PSA nadir of <0.1 ng/mL, which remained durable at the data cut-off in 26 patients (52%).

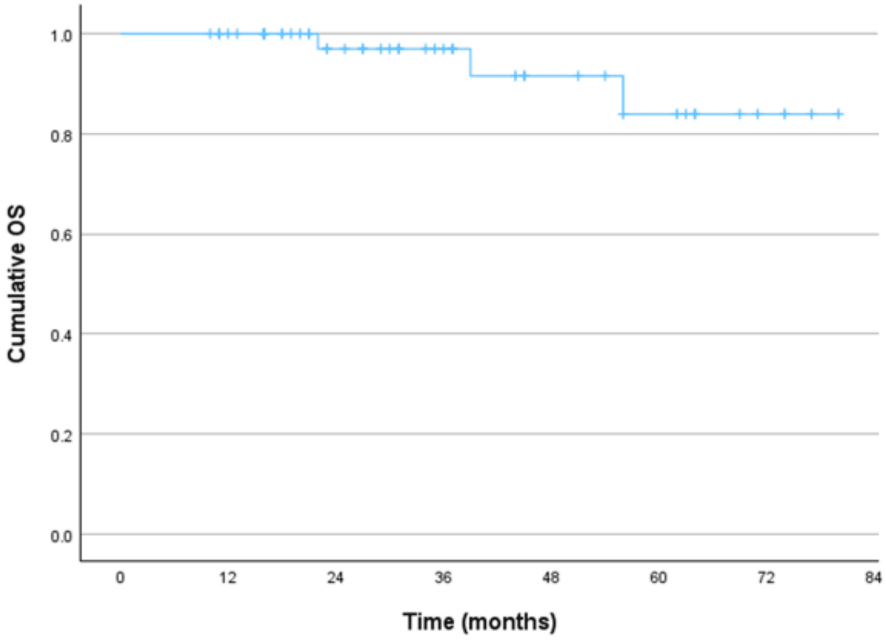


FIGURE 1: Overall survival of the overall population

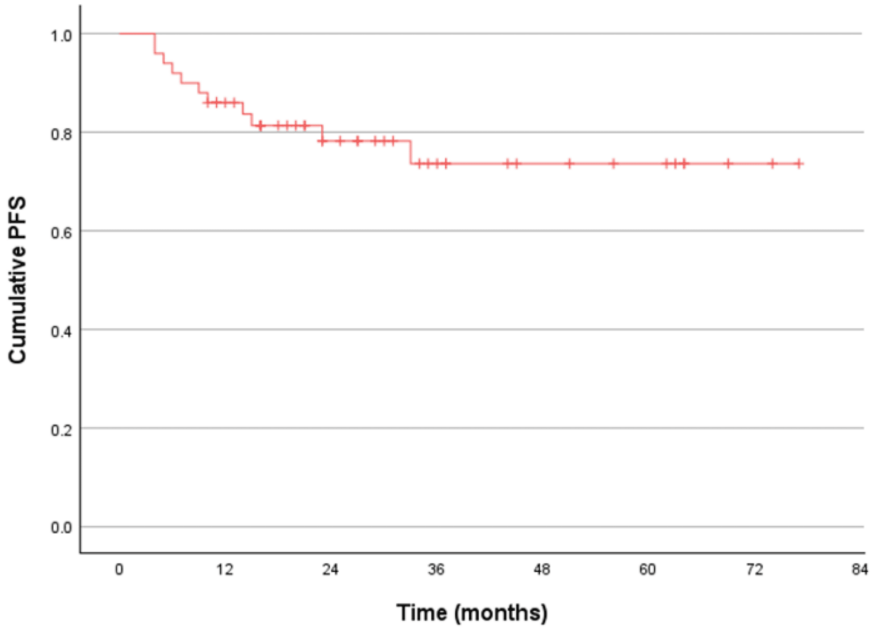


FIGURE 2: Progression-free survival of the overall population

Prognostic factors

Prognostic analyses were restricted to PFS given the excellent OS observed in the current cohort. On univariate log-rank analysis, statistically significant favorable prognostic factors for PFS included non-T4 stage (T1-3 vs. T4, two-year PFS 86% vs. 50%, p=0.017), low PSA value at six months post-radiotherapy (p<0.001), PSA <0.2 ng/mL at six months post-radiotherapy (p=0.001), and low absolute PSA nadir (p<0.001). Notably, the two-year PFS for patients achieving a PSA < 0.2 ng/mL at six months post-radiotherapy was significantly superior to that of patients with a PSA ⩾ 0.2 ng/mL on univariate Cox regression analysis (96% vs. 61%; HR 0.07, 95% CI 0.01-0.57, p=0.013; Figure 3).

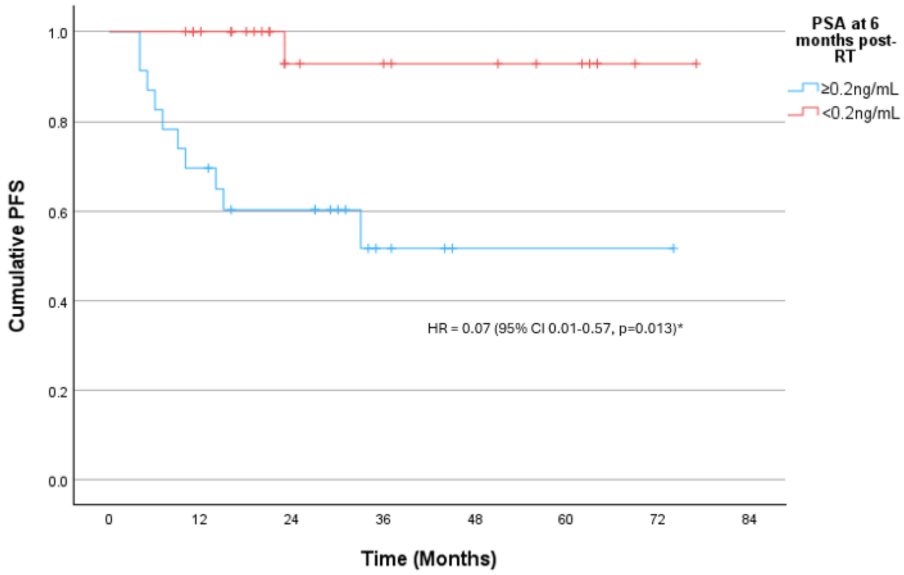


FIGURE 3: Progression-free survival of patients with PSA <0.2 ng/mL and ≥0.2 ng/mL at six months post-RT

PSA: prostate-specific Antigen; RT: radiotherapy

* By univariate Cox regression analysis

Since the prognostic factors PSA at six months, PSA <0.2 ng/mL at six months, and PSA nadir are co-dependent in reflecting a deep biochemical response, PSA <0.2 ng/mL at six months was selected as the most clinically relevant prognostic factor to be included in the primary multivariate analysis model. In view of only 11 events for PFS, a parsimonious multivariate analysis model including only the other significant prognostic factor (non-T4 stage) from univariate analysis was used, and such multivariate analysis is considered exploratory. In this exploratory model, PSA <0.2 ng/mL at six months remains a significant prognostic factor independent of the local stage (HR 0.08, 95% CI 0.01-0.67, p=0.019), whereas T4 stage is statistically insignificant (HR 2.71, 95% CI 0.78 - 9.43, p=0.12; Table *2*).

Factor	Univariate log-rank analysis	Multivariate analysis		
	p value	HR	95% CI	p value
ECOG	0.188	-	-	-
Smoking	0.586	-	-	-
Gleason group	0.286	-	-	-
T stage (T4 vs. non-T4)	0.017	2.71	0.78-9.43	0.12
N stage	0.243	-	-	-
M stage	0.220	-	-	-
Number of bone metastases	0.703	-	-	-
Radiotherapy to pelvic lymph node	0.203	-	-	-
High-dose RT to bone metastasis	0.537	-	-	-
Baseline PSA	0.988	-	-	-
PSA <0.2 ng/mL at 6 months post-RT	0.001	0.08	0.01-0.67	0.019
PSA at 6 months	<0.001	-	-	-
PSA nadir	<0.001	-	-	-

TABLE 2: Univariate and multivariate analyses of prognostic factors for progression-free survival

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PSA = prostate specific antigen; RT = radiotherapy; TNM stage = tumor, node, metastasis stage

Discussion

Despite omitting upfront systemic intensification, our cohort achieved a two-year PFS of 82%. The favorable PFS likely stems from the low baseline metastatic volume of our cohort: 38% had M1a disease, and the majority of M1b patients had solitary bone metastasis. These results underscore the utility of rigorous case selection using PSMA PET-CT to identify patients with truly low metastatic burden, particularly in those with restricted nodal disease or solitary skeletal lesions, where reasonable PFS could be achieved with ADT monotherapy. Conversely, patients staged with conventional imaging may harbor occult, higher-volume disease, necessitating intensified systemic therapy. This may explain why a PFS benefit from local radiotherapy was restricted to the abiraterone-intensified cohort in PEACE-1 [8]. Although the absolute number of bone metastases was not a significant prognostic factor in our study, the vast majority of patients (72%) had 0 or 1 metastasis. Thus, these findings cannot be broadly generalized to all patients falling under the CHAARTED low-volume definition, such as those with a higher number of bone metastases limited to the axial skeleton. While the PFS result is encouraging for patients who opt not for intensive systemic treatment, upfront chemotherapy and/or ARPI still remain the gold standard with proven OS benefit, and are not replaceable by ADT monotherapy should patients opt for upfront intensification.

While PSMA PET-CT represents the contemporary staging gold standard, false-positive interpretations in bone and nodal lesions remain a pitfall [17]. Misclassifying localized or locally advanced disease as low-volume metastatic disease can artificially inflate PFS outcomes following local prostate radiotherapy. Though frameworks such as miTNM (PROMISE) [18] and PSMA-RADS [19] standardize reporting, they are not universally adopted, and both feature equivocal or indeterminate categories left to clinicians' interpretation. Nevertheless, the high specificity and positive predictive value (PPV) of diagnostic PSMA PET-CT are well-documented; a meta-analysis of 266 patients reported a specificity of 0.96 and a PPV of 0.93 [20]. Using PSMA PET-CT to define volume status that was developed originally from conventional imaging may also lead to the Will Roger phenomenon of stage migration, but both up-staging and down-staging have been reported [21]. Therefore, there remains a big knowledge gap on whether treatment effects in low-volume disease defined by traditional imaging are applicable to PET-CT-defined disease. Notably, even for patients with false-positive bone metastases, a de-escalated approach remains clinically sound - though non-standard - as it still delivers the definitive local radiotherapy and long-term ADT utilized in high-risk localized disease. However, these patients face potential overtreatment with lifelong ADT rather than a definitive 18-36 month course, or undertreatment through the omission of an adjuvant ARPI.

Our cohort demonstrates that a PSA <0.2 ng/mL at six months post-radiotherapy serves as a significant

predictor of prolonged PFS. The prognostic value of PSA nadir is well-established in the contexts of ADT monotherapy [22] and ADT + docetaxel combination therapy [23], where a nadir of ⩽0.2 ng/mL strongly correlates with extended survival. In the contemporary era of upfront ARPI regimens, deep PSA declines (<0.2 ng/mL in TITAN [24] and ultra-low <0.02 ng/mL in ARANOTE [25]) continue to predict superior PFS and OS. Contextualized within historical ADT monotherapy data, our cohort achieved a similar rate of deep biochemical response to the SWOG 9346 trial, where 45% of patients reached a PSA ⩽0.2 ng/mL by month 7 compared to 60% in our study, corroborating its value as an early surrogate for PFS [22]. The six-month post-radiotherapy assessment window is also clinically actionable: 19 of the 23 patients (83%) in our cohort who had a PSA ⩾0.2 ng/mL at six months subsequently experienced further delayed PSA declines rather than immediate progression. Given their higher statistical risk of progression, this six-month landmark could be potentially utilized in future prospective studies to investigate the strategy of systemic re-intensification (e.g., adding an ARPI) to delay progression to castration-resistant disease for patients having a PSA ⩾0.2 ng/mL at six months after RT. While absolute PSA nadir was also a significant prognosticator, it functions primarily as a retrospective marker and is less useful for real-time clinical decision-making.

Four patients without histological confirmation or verifiable biopsy record were included in the study for analysis since they had high baseline PSA (22.6 - 391 ng/mL), had lesions with high PSMA uptake of at least a maximum standardized uptake value (SUVmax) of 10, and demonstrated good biochemical response to local RT and ADT monotherapy with PSA nadir of 0-0.6 ng/mL, reflecting a typical profile of acinar adenocarcinoma subtype. Although any component of small cell or neuroendocrine tumor may be missed and may exaggerate PFS events, such histology is rare, associated with low PSA on presentation and lesions with low PSMA uptake, and generally demonstrates poor response to ADT alone [26,27]. Since three out of four of these patients still remained progression-free at data cut-off, any effect or bias on PFS exaggeration is small. While such justification is retrospective, a repeat univariate analysis excluding these four patients without biopsy confirmed both non-T4 stage (p=0.046) and PSA <0.2 ng/mL at six months post-RT (p=0.002) to be significant favorable prognostic factors.

Combining metastasis-directed SBRT with primary prostate radiotherapy for limited osseous lesions represents an attractive strategy to support systemic de-escalation. The efficacy of metastasis-directed therapy (MDT) was initially demonstrated in the STOMP [28] and ORIOLE [29] trials, which showed extended ADT-free survival following SBRT for oligometastatic recurrences, though these studies evaluated metachronous rather than de novo disease. In the EXTEND trial [30], which included both castration-sensitive and castration-resistant cohorts, combining MDT with intermittent hormone therapy (a form of de-escalation) significantly prolonged PFS compared to continuous hormone therapy alone. While upfront MDT is not currently standard in low-volume mHSPC, it is an appealing option when systemic de-escalation is pursued. In our cohort, five patients (10%) with solitary bone metastases received high-dose radiation to the osseous lesion. Although more favorable PFS outcomes are expected for these patients, resulting in bias towards better PFS, two out of five have progressed at the time of data cut-off, while high-dose bone radiotherapy was not a significant prognosticator of PFS on univariate analysis (p=0.537), again echoing the inherently favorable disease nature of this cohort from its limited disease burden defined by PSMA PET-CT and the observation that a reasonable PFS could be achieved without intensive systemic treatment and radiotherapy to bone metastases. As this finding is limited by the small sample size and number of patients receiving MDT, prospective randomized trials are required to define the benefit of adding upfront MDT in de novo, low-volume mHSPC.

Limitations

This study is constrained by its single-center framework and relatively brief follow-up period. In view of the retrospective nature, there were inconsistencies regarding radiotherapy protocol and patient selection for pelvic nodal irradiation and metastasis-directed radiotherapy, with potential bias. The limited number of survival and progression events increases the susceptibility of multivariate analysis to mathematical overfitting, such that these exploratory findings should be interpreted cautiously.

Additionally, variations in long-term PSA monitoring intervals and differing clinical thresholds for ordering restaging PSMA PET-CT scans to detect early radiographic progression prior to a standard 2 ng/mL PSA rise may have influenced progression timelines. Extended follow-up is mandatory to confirm the prognostic value of PSA <0.2 ng/mL six months post-radiotherapy and whether it translates into an OS benefit.

Conclusions

While systemic intensification represents the current standard of care for mHSPC, our real-world cohort demonstrates that for patients who are staged with PSMA PET-CT and cannot receive or tolerate such treatments, pairing prostate radiotherapy with de-escalated ADT monotherapy yields favorable PFS and OS, which must be interpreted as preliminary and observational given our sample size and limited event counts. A six-month post-radiotherapy PSA threshold of <0.2 ng/mL is a prognostic marker that could be further explored in prospective trials for systemic treatment re-intensification strategies. Longer follow-up and prospective studies are required to validate this threshold as an independent prognostic factor.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Yuen Hang Lau

Acquisition, analysis, or interpretation of data: Yuen Hang Lau, Chung Hang James Chow

Drafting of the manuscript: Yuen Hang Lau

Critical review of the manuscript for important intellectual content: Chung Hang James Chow

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Hospital Authority Central Institutional Review Board issued approval CIRB-2026-123-4. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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