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GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Trends in Management of Oligometastatic Hormone-Sensitive Prostate Cancer

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Abstract

Purpose of Review Systemic therapy for patients with hormone-sensitive oligometastatic prostate cancer is non-curative and associated with toxicities. Meanwhile, this population presents unique clinical opportunities to improve outcomes, including the demonstrated benefits of radiotherapy to the primary tumor or oligometastatic sites.

Recent Findings Recently published randomized studies have demonstrated benefits with the addition of radiotherapy to the primary disease or metastatic lesions in patients with synchronous or metachronous disease. The introduction of novel PET imaging has improved the sensitivity and specificity for detecting metastatic disease and provides an opportunity to better select patients who will benefit from local therapy.

Summary The data presented in this review supports revisiting practice guidelines for patients with hormone-sensitive metastatic prostate cancer, particularly in relation to the role of radiotherapy to the primary tumor and sites of oligometastatic disease. Future trials will aim to further establish the role of metastasis-directed therapies in metachronous, synchronous, and castrate-resistant disease.

Keywords Oligometastases · Metastasis directed therapy · SBRT · Prostate cancer

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Introduction

Oligometastatic cancer represents a state between localized and widespread metastatic disease and has been specifically described in prostate cancer [1, 2]. While no universal definition of oligometastatic disease exists, at the 2017 Advanced Prostate Cancer Consensus Conference (APCCC), oligometastatic disease was defined as the presence of three or fewer bone or lymph node metastases [3], although often patients with up to five metastases are included in clinical trials. Despite the uncertainty regarding its definition, its relevance as a separate entity is increasingly being recognized as evidence grows for the treatment of limited metastatic lesions with metastasis-directed therapies (MDTs) such as stereotactic body radiation therapy (SBRT) and surgery, either in combination with or prior to systemic therapies [4]. The argument for aggressive local treatment of patients with metachronous disease is supported by recent study findings of whole-genome sequencing in prostate cancer that suggest indolent metastatic lesions have the potential to transform and become aggressive foci of accelerated metastasis [5, 6]. Therefore, treating metastatic lesions may potentially alter the natural history of metastatic disease by delaying disease progression and may ultimately improve survival outcomes. Additionally, MDT allows for delay in systemic therapies and associated toxicities, thereby improving patient quality of life (QOL) [7•]. Most recently, promising results of the Phase II randomized study SABR-COMET, which included patients with prostate cancer, were presented and showed improved overall survival (OS) in patients randomized to the SBRT plus standard of care (SOC) arm compared to SOC alone (41 months versus 28 months, $p = 0.09$) [4]. In this review, we therefore aim to appraise recent evidence for treatment options for patients with hormone-sensitive oligometastatic disease, including management of regional nodal disease, systemic and local options for metastatic disease, and summary of imaging modalities in these settings.

De Novo Nodal-Only Oligometastatic Prostate Cancer

Patients with suspicious lymph nodes on imaging at initial diagnosis of prostate cancer represent approximately 10% of newly diagnosed cases, with this number likely to increase with the increased utilization of advanced imaging techniques [8]. The presence of regional nodal disease is typically associated with poor prognosis. While no longer defined as M1 by the AJCC 8th TNM Staging 8th Edition, it is currently regarded as Stage IV disease and historically was treated with palliative intent systemic therapies [9]. Increasingly, evidence suggests that these patients should be treated with curative intent, with local therapy playing a role in improving clinical outcomes; however, this question is yet to be addressed in a randomized clinical trial. The strongest evidence that supports the role of radiotherapy in this setting is from a post hoc analysis of the control arm of the STAMPEDE trial [10]. The authors report on failure-free survival on a selected group of patients from the control arm ($n = 1858$), who had clinically node-positive disease at diagnosis and greater than 1-year follow up data ($n = 177$). All patients in this group had ADT; however, radiotherapy was as per physician choice. In total, 97 patients were planned to receive radiotherapy and 80 were planned to receive no radiotherapy. Of the patients who ultimately received radiotherapy ($n = 78$), 82% received radiotherapy to both the prostate and the pelvic lymph nodes. The 2-year failure-free (biochemical or radiological) survival as per planned radiotherapy treatment was better in the radiotherapy arm (81%, 95% CI 71–87%) compared to the no radiotherapy arm (53%, 95% CI 40–65%). RTOG late grade ≥ 3 toxicity was low, with only 2% of patients experiencing grade 3 hematuria. The results of this trial are supported by a SEER database analysis of 3787 patients with node-positive prostate cancer who received either ADT alone or ADT plus local therapy between 1995 and 2005 [11]. Patients were further subdivided into patients who were clinically node positive ($n = 796$) and pathologically node positive ($n = 2991$). Of the clinically node-positive patients, 43% received external beam radiotherapy (EBRT) and had a significantly higher 10-year OS compared to patients who did not receive EBRT (45% vs. 29%, $p < 0.001$). Similarly, in the pathologically node-positive cohort, 78% of patients received local therapy (radical prostatectomy, EBRT or a combination) and had a higher 10-year OS compared to the no local therapy group (65% vs. 42%, $p < 0.001$). There was no OS difference seen between patients who received surgery versus radiotherapy.

Systemic Treatment Options for Oligometastatic Disease

The current SOC for hormone-sensitive de novo metastatic prostate cancer is androgen deprivation therapy (ADT) given with either docetaxel or abiraterone. The randomized CHAARTED trial first showed an OS benefit from the addition of docetaxel to ADT (median OS 57.6 months with docetaxel vs 44.0 months with ADT alone, $p < 0.001$) [12]. A pre-defined subgroup analysis of long-term data subsequently found docetaxel to have an OS advantage in patients with high volume (presence of visceral metastases and/or ≥ 4 bony metastases with at least one bony metastasis outside the spine or pelvis) but not low-volume disease [13]. The survival benefit from the addition of docetaxel in men with hormone-sensitive high risk or metastatic prostate cancer was further supported by the results of the randomized multi-arm STAMPEDE trial, in which the addition of docetaxel to SOC improved OS

(median OS 71 months versus 81 months, HR 0.78, 95% CI 0.66–0.93, p 0.006), with no evidence of heterogeneity in treatment effect in patients with node negative versus node positive and M0 versus M1 disease [14]. The survival benefit of abiraterone in metastatic hormone-sensitive prostate cancer was also shown in two randomized trials, STAMPEDE [15] and LATITUDE [16], with no evidence of heterogeneity of treatment effect according to metastatic status shown in STAMPEDE which included both high-risk non-metastatic and metastatic patients.

While most of the above trials allowed patients with both synchronous and metachronous metastatic prostate cancer, the latter group formed a small percentage of patients included within the studies and is a group generally believed to have an improved prognosis compared to patients with synchronous disease. The results of these studies therefore should be extrapolated with caution to patients with recurrent disease. Furthermore, while ADT typically forms the backbone of treatment for patients with recurrent disease, the timing of ADT (immediate versus deferred) in patients with low-volume asymptomatic metastatic disease or biochemical recurrence without metastases on conventional imaging remains controversial, with randomized trials reflecting some uncertainty on whether immediate ADT confers an OS benefit in all patients within this group [17–21].

Nevertheless, once ADT is commenced, it is usually lifelong and often associated with toxicity. In fact, grade 3 toxicity was experienced by 33% of patients in the ADT only arm, and 47% of patients in the ADT plus abiraterone arm in the STAMPEDE trial [15], with even higher rates of grade 3 toxicity seen in the LATITUDE trial (48% in the ADT arm and 63% in the ADT plus abiraterone arm) [16]. Furthermore, patients with hormone-sensitive disease usually develop castrate-resistant prostate cancer (CRPC) within 18 to 36 months of treatment commencement [22]. The possible advantages of offering patients MDT prior to or combined with systemic therapy therefore include to delay initiation of lifelong systemic treatment and its associated toxicities, to delay the onset of CRPC and to improve survival outcomes.

Local Therapies for Synchronous Oligometastases

While systemic treatment remains the SOC for most patients with metastatic disease, the value of cytoreductive treatment of the primary disease has been established in patients with cancers other than prostate cancer [23, 24]. The rationale for obtaining control of the primary tumor in metastatic disease includes eliminating a primary source of metastasis [25], prevention of cytokine signaling from the primary which may lead to increased metastatic seeding [26, 27], and for local symptom control.

The results of the first reported randomized trial that assessed the potential benefit of local radiotherapy to the prostate in patients with metastatic disease, HORRAD, assessed the survival benefit of prostate radiotherapy in addition to ADT in patients with bone only metastatic prostate cancer but did not show a statistically significant OS benefit with the addition of radiotherapy (median OS of 45 months in the radiotherapy arm versus 43 months in the control arm, $p = 0.4$) (see Table 1) [28•]. Of the 432 patients included in HORRAD study, 67% of patients had greater than five metastatic sites of disease, 40% had >Gleason 8 disease, 25% had cT4 disease, and over 50% of patients had a baseline PSA of > 125. In an unplanned subgroup analysis, the effect size for survival was greater in patients with a lower burden of metastatic disease (<five bone metastases, HR 0.68, 95% CI 0.42–1.10), generating the hypothesis that improved patient selection may have resulted in a survival benefit from local radiotherapy.

The second randomized trial to publish in this area is the STAMPEDE trial (arm H), which also aimed to assess the benefit of local radiotherapy in the setting of newly diagnosed metastatic prostate cancer [29•]. The trial included a pre-planned subgroup analysis of patients with low versus high burden of metastatic disease, which was defined as per the CHAARTED trial, with high burden being patients with ≥ four sites of bony metastases with at least one metastasis located outside of the spine and pelvis and/or patients with any number of visceral metastases. The study recruited in total 2061 patients, with 1029 receiving ADT (plus Docetaxel in 18% of patients) and 1032 receiving EBRT to a dose of 55 Gy in 20 fractions over 4 weeks, or 36 Gy in 6 fractions over 6 weeks. Median follow up for the study was 37 months (IQR 24–48 months). Analysis of the entire study population revealed improved failure-free survival (HR 0.76, 95% CI 0.68–0.84, $p < 0.0001$); however, no OS benefit (HR 0.92, 95% CI 0.80–1.06, $p = 0.266$) to the addition of radiotherapy. A pre-specified subgroup analysis of the low metastatic burden group ($n = 819$) revealed improved OS (HR 0.68, 95% CI 0.52–0.90, $p = 0.007$) and failure-free survival (HR 0.59, 95% CI 0.49–0.72, $p < 0.0001$) secondary to radiotherapy. The effect size for OS for the low metastatic burden group was similar to that reported in the HORRAD study. Severe acute and late radiotherapy-related toxicity of RTOG ≥ grade 3 was seen in only 5% and 4% of patients respectively.

The results of these prospective studies are supported by prior retrospective reports. A number of retrospective studies suggest that the benefit of local treatment is greater in patients with a lower burden of disease [30–36]. In particular, these studies suggested that the survival benefit from local treatment was greatest in patients with lower baseline PSA values, lower T stages, nodal only metastases, and lower Gleason scores. While many of these studies also suggested benefit of local treatment in patients with both lower and higher burden of disease, this was not seen in the prospective trials and may

Table 1 Synchronous oligometastases

First author (year)	Study design	Number of patients	Treatment	Oncological outcomes	Median follow up	Toxicity
Boeve (2018) HORRAD	Randomized phase III	432 (67% had > 5 bone metastases)	ADT ± Prostate RT	Median OS 43 months (no RT) versus 45 months (with RT), HR 0.43, 95% CI 0.17–1.05, $p = 0.063$ OS (in patients with < 5 bone metastases): HR 0.68, 95% CI 0.42–1.10	47 months (IQR 36–68 months)	Not reported
Parker (2018) Arm H of STAMPEDE	Randomized phase III	2061 (1091 ADT, 1032 EBRT + ADT) 819 patients with low metastatic burden	ADT ± Prostate RT	Improved failure-free survival in RT group (HR 0.76, 95% CI 0.68–0.84, $p < 0.0001$) No OS benefit in RT group (HR 0.92, 95% CI 0.80–1.06, $p = 0.266$) Subgroup analysis low metastatic burden group ($n = 819$) revealed improved OS in RT group (HR 0.68, 95% CI 0.52–0.90, $p = 0.007$)	37 months (IQR 24–48 months)	Acute and late radiotherapy related toxicity of > grade 3 in 5% and 4% of patients respectively RTOG toxicity criteria
Poelaert (2017) LoMP	Prospective, non-randomized	46	29 standard of care alone, 17 standard of care + RP	At 3 months, 5 (29.4%) patients in surgery group reported stress urinary incontinence without any further local symptoms. Standard of care group: 2 (6.8%), 11 (37.9%), and 2 (6.8%) patients suffered urge incontinence, obstructive voiding and ureteric obstruction respectively	Outcomes and toxicity reported at 3 months	Surgical group: 11.8% grade II Clavien classification
Loppenberg (2017)	Retrospective National Cancer Database analysis 2004–2012	15,501	ADT + local therapy (RP or RT) vs. no local therapy (1470 received local therapy—77% EBRT, 20% RP, 3% brachytherapy)	3-year OS 69% (local therapy) vs. 54% (no local therapy), $p < 0.001$	39 months	Not reported
Leyh-Bannurah (2017)	Retrospective SEER database analysis 2004–2013	474 (local therapy) 1896 (no local therapy, used for propensity score matched analysis)	ADT ± local therapy (313 RP, 161 brachytherapy, note patients undergoing EBRT excluded from this analysis as site of EBRT not recorded)	Lower cancer specific mortality in local therapy group (sub-HR 0.40, 95% CI 0.32–0.50)	No local therapy: 31.0 months (IQR 12.0–58.0) Local therapy: 43.5 (IQR 18.0–80.0)	Not reported
Satkunasivam (2015)	Retrospective SEER-Medicare database analysis 2004–2009	4069 patients with metastatic prostate cancer > 65 years old	ADT with or without local therapy (RP $n = 47$, IMRT $n = 88$, CRT $n = 107$)	RP: 52% reduction in risk of CSM (HR 0.48, 95% CI 0.27–0.85) IMRT: 62% reduction in risk of CSM (HR 0.38, 95% CI 0.24–0.61) CRT: no improved survival	20 months (IQR: 10–36)	Not reported
Gratzke (2014)	Retrospective Munich Cancer Registry	1538	ADT ± RP ($n = 74$)	5-year OS: RP 55% vs no RP 21%, $p < 0.01$	Not reported	Not reported

ADT androgen deprivation therapy, *RT* radiotherapy, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *IQR* interquartile range, *EBRT* external beam radiotherapy, *RTOG* radiation therapy oncology group, *RP* radical prostatectomy, *SEER* surveillance, epidemiology and end results, *IMRT* intensity modulated radiotherapy, *CRT* conformal radiation therapy, *CSM* cancer-specific mortality

be due to the risk of selection bias, and an inability to control for confounders often inherent to retrospective and population-based analyses.

Overall, the current body of literature suggests that the addition of radiotherapy to the primary confers a survival advantage in patients with synchronous low-volume metastatic prostate cancer. The role of surgery to the primary, as well as local therapy to sites of metastatic disease in the synchronous context, is yet to be formally tested and we await the results of a number of upcoming trials to shed further light on these issues.

Management Options for Metachronous Oligometastases

Metachronous oligometastases or oligorecurrent prostate cancer refers to the phenomenon of relapsed metastatic disease appearing following curative treatment of the primary disease. Distinguishing metachronous from synchronous disease is important as the status of the primary tumor is shown to be a significant factor in predicting outcome, with patients with controlled primary tumors performing better [37, 29•]. Lymph nodes are commonly identified as a site of failure in prostate cancer, particularly in the post radical prostatectomy treatment setting, followed by distant bony metastatic disease [38, 39].

Salvage Lymph Node Dissection

In patients with oligorecurrent disease presenting with involved pelvic lymph nodes, salvage lymph node dissection (sLND) is a treatment option, although the data that supports this strategy is limited to retrospective studies. These data, which include a systematic review of 12 studies with 480 cases of sLND, show biochemical response rates ranging from approximately 20% to 80% (see Table 2) [40–48]. In the majority of patients, however, this response is not sustained with 2- to 5-year biochemical relapse-free (BCR) survival reported to be 19% to 31% [41, 42, 47] with the largest series including 654 patients reporting 150 patients experienced early clinical recurrence at 1 year [48]. Two studies reported on rates of complete biochemical response with undetectable PSA levels following surgery of 28% to 46% and in these patients, the 1-year and 3-year BCR-free survival rates were higher at 72% and 69% respectively [40, 49]. In addition, patients with lower Gleason scores at time of radical prostatectomy, lower PSA values at time of sLND, and fewer lymph nodes and lack of retroperitoneal nodal disease following sLND had lower rates of clinical recurrence [45, 47, 49]. This suggests that in an appropriately selected cohort of patients, sLND may result in long-term disease control.

Stereotactic Body Radiation Therapy

A systematic review published in 2018 assessed the value of stereotactic body radiation therapy (SBRT) in treating nodal only oligorecurrent prostate cancer [50]. A total of 9 studies with 363 patients were included, with 211 patients treated with SBRT to 270 lymph nodes. With a median follow up of 19.2 months, local control was 98.1%. Median PFS, defined as radiological and/or biochemical control, was 22.5 months (range 11–30 months). Forty-one percent of patients were on ADT at the time of SBRT. For patients that did not receive ADT, the median ADT-free survival was 32.8 months (range 25–44 months). The rate of toxicity was low, with an overall ≥ Grade 2 acute or late toxicity of 5.6%.

Two completed prospective studies have investigated the role of SBRT in patients with metachronous oligometastatic prostate cancer, including both nodal and distant metastatic disease (see Table 2) [7•, 51•]. The first reported study, titled the Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP), was a prospective randomized phase II study that compared MDT to surveillance [7•]. Patients were included if they had biochemical relapse following curative intent treatment of localized prostate cancer and had one to three sites of metastatic disease defined by choline positron emission tomography computed tomography (PET/CT). The primary endpoint of the study was ADT-free survival, with ADT commenced only for symptomatic progression, local progression, or progression to greater than three metastases. In total, 62 patients were enrolled, and of these 34 had nodal disease, 24 bony disease, 3 bony and nodal disease, and 1 patient had non-bony distant metastasis. Of the 31 patients randomized to MDT, 25 patients received 30 Gy in 3 fractions, while 6 patients underwent surgery (five patients underwent salvage lymph node dissection (sLND) and one patient underwent lung metastasectomy). Median follow up for the study was 3 years (IQR 2.3–3.8 years). Study findings revealed that ADT-free survival was higher in the MDT arm compared to the active surveillance arm (21 months versus 13 months, HR 0.60, 80% CI 0.4–0.9, $p = 0.11$). No local or symptomatic progression was observed in the MDT arm, with six and three patients with progression respectively observed in the active surveillance arm. Eleven patients on the MDT arm underwent further MDT for oligometastatic progression, and 19 patients in total commenced ADT for polymetastatic progression. MDT appeared to have a greater magnitude of effect in patients with a PSA doubling time of less than 3 months compared to greater than 3 months (p value for interaction = 0.01). The median time to PSA progression in the MDT arm was 10 months compared to 6 months for the surveillance group (HR 0.53, 80% CI 0.37–0.77, $p = 0.03$). Overall treatment was very well tolerated with 17% of patients experiencing grade 1 toxicity and no ≥ grade 2 toxicity noted. Patient reported health related

Table 2 Metachronous oligometastases

First author (year)	Study design	Number	Treatment	Oncological outcomes	Median follow up	Toxicity
Nodal only disease treated with salvage lymph node dissection						
Fossati (2019)	Retrospective	654 patients	Salvage lymph node dissection	Early clinical recurrence at 1 year in 150 patients. Median time to progression 18 months	30 months (in patients without clinical recurrence)	Not reported
Porres (2017)	Retrospective	87 patients	Salvage lymph node dissection	Complete BR 28% BR 41%	21 months	6 Grade II 8 Grade III Clavien classification
Zattoni (2016)	Retrospective	117 patients	Salvage lymph node dissection	BR 80% 5-year biochemical recurrence-free survival 31%	20 months	10 Grade II 6 Grade III 1 Grade IV Clavien classification
Oderda (2016)	Retrospective	106 patients	Salvage lymph node dissection	BR 51% 2-year biochemical recurrence-free survival 25%	23 months	10 Grade II 10 Grade III Clavien classification
Suardi (2015)	Retrospective	59 patients	Salvage lymph node dissection	BR 59% 8-year clinical recurrence-free survival 38% 8-year biochemical recurrence-free survival in patients with a complete BR 23%	81 months	13 Grade II 11 Grade III Clavien classification
Tilki (2015)	Retrospective	58 patients	Salvage lymph node dissection	BR 22% Clinical recurrence 48% 5-year cancer specific survival 71%	39 months	Not reported
Rigatti (2011)	Retrospective	72 patients	Salvage lymph node dissection	BR 57% 5-year biochemical recurrence free survival 19% 5-year clinical recurrence free survival 34%	40 months	17 Grade II 16 Grade III Clavien classification
Nodal or distant metastatic disease treated with metastasis directed therapy						
Ost (2018) STOMP	Phase II randomized multicenter	62 patients (24 bone, 1 lung, 34 node, 3 node + bone)	Randomized to MDT (surgery/SBRT 30 Gy in 3 fractions) vs. surveillance (1:1)	Median ADT-free survival: 21 (MDT) vs 13 months (HR 0.60, 80% CI 0.40–0.90, p = 0.11)	3 years (IQR 2.3–3.75 years)	17% grade 1 toxicity in MDT arm, no grade 2–5 CTCAE v4.0 or Clavien classification (surgical patients)
Siva (2018) POPSTAR	Prospective single arm	33 patients (20 bone, 12 node, 1 bone and node)	Single fraction SBRT (20 Gy)	97% completed planned treatment. 2-year LPFS: 93%, (95% CI 84–100%) 2-year DPFS: 39% (95% CI 25–60) 2-year ADT-free survival: 48%	All patients followed up for 2 years	3% grade 3 toxicity CTCAE v4.0
Tran (2018) ORIOLE	Phase II randomized (abstract only of interim analysis)	36 patients (out of target 54)	Randomized to SBRT vs observation (2:1)	Progression at 6 months: 67% in observation vs 33% in SBRT arm	All patients followed up for 6 months	No > grade 3 toxicity on SBRT arm CTCAE v4.0
Kneebone (2018)	Registry study	57 patients, 73 lesions (37 lymph nodes only, 18 bone only, 2 bone and lymph nodes)	SBRT (20 Gy in 1 fraction or 24 Gy in 2 fractions to bone; 50 Gy in 5 fractions or 30 Gy in 3 fractions to nodes)	Median biochemical disease-free survival: 11 months Biochemical failure: 43 patients Local control: 100%	16 months	Acute: 4 Grade 1 1 Grade 2 Late: 5 Grade 1

Table 2 (continued)

First author (year)	Study design	Number	Treatment	Oncological outcomes	Median follow up	Toxicity
Decaesteck-er (2014)	Retrospective	50 patients, 70 lesions (54% lymph nodes, 44% bone, 2% viscera)	SBRT (50 Gy in 10 fractions + 1-month ADT OR 30 Gy in 3 fractions)	Median PFS: 19 months (95% CI 13–25) Median ADT-free survival 25 months (95% CI 20–30) 2 and 5-year CSS 96% and 90% respectively	2 years	7 Grade 1 3 Grade 2 CTCAE v3.0
Jereczek-Fo-ssa (2017)	Retrospective	94 patients (124 lymph nodes)	SBRT ± ADT in 34 patients (median dose 24 Gy in 3 fractions)	BR 68% 2-year LC 84% 2-year PFS 30%	18.5 months	Acute: 7 grade 1 or 2 GU 1 grade 1 GI Late: 5 grade 1 or 2 GU *Toxicity grading system not provided
Ost (2016)	Retrospective	119 patients, 163 lesions (72 lymph nodes, 43 bone, 4 viscera)	SBRT (modal BED 120–139 Gy) ± ADT (60 patients)	3- and 5-year LPFS 93% and 92% Median DPFS: 21 months (95%CI 15–26) Median ADT free time: 28 months (95% CI 16–70) 3 and 5-year OS: 95% and 88% respectively	3 years (IQR: 1.75–4)	Late: 17 patients grade 1 toxicity 3 patients grade 2 toxicity CTCAE v4.0
Pichhio (2014)	Retrospective	83 patients (lymph nodes only)	HTT (36–74 Gy in 28 fractions) ± ADT (70%)	Of the 94 HTT treatments, 66 had a complete BR, 12 had a partial response, 1 had stable disease immediately after HTT. Of 47 patients that had repeat PET post HTT, 20 had a complete response, 22 a partial response, 3 had progressive disease, 2 had stable disease.	Oncological outcomes reported for patients immediately post HTT. Patients followed for 3 months post HTT for acute toxicity reports.	≥ grade 2 acute toxicity: Grade 2 GU: 3% Grade 2 GI: 4% Grade 2 rectal: 3% Grade 2 skin: 1% Grade 3 GU: 2% RTOG toxicity criteria
Muldermans (2016)	Retrospective	66 patients, 81 lesions (74 bone, 6 lymph node, 1 liver)	SBRT (Median dose 16 Gy in 1 fraction)	2-year metastasis control 82% bPFS 54% DPFS 45% OS 83%	16 months (range 3–49)	Acute: 2 grade 2 pain flare Late: No ≥ grade 2 toxicity CTCAE v4.0
Triggiani (2017)	Retrospective	100 patients, 139 lesions (117 lymph node, 22 bone)	SBRT (median BED, α/β ratio = 3, 116 Gy, range 80–217)	2-year DPFS 43% 2-year LC: 93% Median ADT-free survival: 20.9 months	20.4 months	2 grade 2 GU toxicity (acute and late) CTCAE v4.0

BR biochemical response, *MDT* metastasis directed therapy, *SBRT* stereotactic body radiotherapy, *Gy* Gray, *ADT* androgen deprivation therapy, *HR* hazard ratio, *CI* confidence interval, *IQR* interquartile range, *CTCAE* Common Terminology Criteria for Adverse Events, *LPFS* local progression free survival, *DPFS* distant progression free survival, *CSS* cancer-specific survival, *BR* biochemical response, *LC* local control, *GU* genitourinary, *GI* gastrointestinal, *BED* biologically effective dose, *OS* overall survival, *HTT* helical tomotherapy, *RTOG* Radiation Therapy Oncology Group, *bPFS* biochemical progression-free survival

quality of life (QOL) was assessed at baseline, 3 months, and 12 months and was stable over time with no clinically significant difference across the two study arms.

Interim results of a similar randomized study, Observation versus stereotactic ablative Radiation for OLigometastatic prostate cancer (ORIOLE, ClinicalTrials.gov Identifier NCT02680587), reported progression at 6 months to be lower in the SBRT versus observation arm (33% versus 67%) following recruitment of 36 out of a planned 54 patients with oligometastatic hormone-sensitive prostate cancer [52•].

The second prospective study, a pilot study of patients with Oligometastases from Prostate cancer treated with STereotactic Ablative body Radiosurgery (POPSTAR), is a single-arm study which included 33 patients with oligometastatic (1 to 3 lesions) prostate cancer who underwent single fraction SBRT to 20 Gy. In contrast to the STOMP study, the majority of patients had bone only disease ($n = 20$), while 12 patients had nodal disease, and 1 patient had both. This is likely due to the use of sodium fluoride PET to screen patients, which has poor sensitivity and specificity for detecting nodal disease. Patients were followed up for 2 years following treatment. Similar to the previous study, SBRT was tolerable, with 16 CTCAE v4.0 Grade 1, five Grade 2. and one Grade 3 toxicity (vertebral fracture). Local control following SBRT was similarly excellent with 2-year local progression-free survival (PFS) of 93% (95% CI 84–100%), although patients still frequently developed distant disease, with a 2-year distant PFS of 39% (95% CI 25–60%). QOL was stable from baseline to 1 year, although pain-related items were worse at 2 years compared to baseline, likely secondary to out-of-field distant failure. In those not on ADT, the 2-year freedom from ADT was 48%.

These results are supported by the findings of multiple retrospective studies [50, 53, 54]. Furthermore, a single-center registry study of 57 patients with 1–3 metastases detected by PSMA PET reported a median biochemical disease-free survival rate of 11 months after treatment with SBRT, with no in-field failures, and no patients with ≥ grade 2 late toxicity [55]. A recent systematic review published in 2018 summarized the use of SBRT for oligometastatic prostate cancer from any site [53]. This review found a total of 14 studies including 661 patients and 899 lesions (561 nodal, 336 bone, and 2 liver). Two-thirds of patients had high-risk prostate cancer on primary diagnosis. A range of SBRT schedules were used with 30 Gy in three fractions being the most common ($n = 126$). Most of the studies employed choline PET to assess baseline and recurrent disease. Local control rates were high and ranged from 82 to 100%. There were no in-field recurrences when radiotherapy doses delivered exceeded a biologically equivalent dose (BED) of ≥108 Gy ($\alpha/\beta = 3$ Gy). Median ADT-free survival was reported in five studies and ranged from 12.3 to 39.7 months. Two-year PFS was reported in seven studies and ranged from 30 to 64 months. Toxicity within the published series was low, with only one grade 3 acute and two grade 3 late toxicities seen. Of the four studies that clearly documented patterns of failure post SBRT, 20% had lymph node only failure, 13% had bone only failure, 2% had both, 2% had prostate bed, 6% had systemic failure, and 6% had in-field failure.

Overall, the combined results of multiple retrospective and early-phase prospective studies indicate that SBRT in the setting of recurrent oligometastatic disease is safe (see Fig. 1 for case example), with the first phase II randomized controlled trial indicating a potential gain from SBRT over observation alone. Further phase III trials are necessary however before SBRT can be implemented as standard of care in this setting.

Finding the Optimal Imaging Modality for Oligometastatic Disease

The benefits of MDT are critically dependent upon imaging methods that are able to accurately assess oligometastatic disease in order for all disease to be effectively treated and to avoid futile treatment of patients subsequently recognized to have widespread or high-volume metastatic disease. While traditionally CT and ^{99m}Tc-MDP bone scintigraphy have been used for staging and follow up of patients with prostate cancer, they frequently lead to understaging. Meanwhile, modern imaging methods that use PET/CT with tumor-specific radiotracers and whole-body MRI with diffusion-weighted imaging offer better imaging performance that can improve patient selection [56].

Traditional imaging methods used in prostate cancer have advantages including being cost-effective and widely accessible. However, while CT allows for whole-body soft tissue imaging, it has poor sensitivity and specificity for detection of lymph node metastases, secondary to difficulty in identifying architectural changes in small lymph nodes and is suboptimal for the detection of bone metastases [57]. Bone scintigraphy is often therefore used in conjunction with CT for detection of bone lesions, with pooled results from a meta-analysis showing bone scintigraphy has a per-lesion sensitivity of 0.59 and specificity of 0.75 for bone metastases [58].

Functional imaging using ^{18}F-sodium fluoride (NaF) PET appears to be superior to bone scintigraphy however is predominantly an indication of osteoblastic activity and regional blood flow and therefore has less utility for detecting soft tissue and lytic bone disease. In one review of 318 patients from eight studies, the weighted mean sensitivity of ^{18}FNaF PET was 96% and specificity was 77% for bone metastases, although in a number of these studies, the reference standard for bone disease was established by incorporating follow-up imaging with CT, bone scintigraphy or MRI, rather than histological confirmation [59]. PET with radiolabeled choline detects cell membrane phospholipid synthesis as a surrogate of cell growth and is one of the most widely used PET tracers in the diagnosis and re-staging of prostate cancer [60]. For bone metastases, ^{18}Fcholine

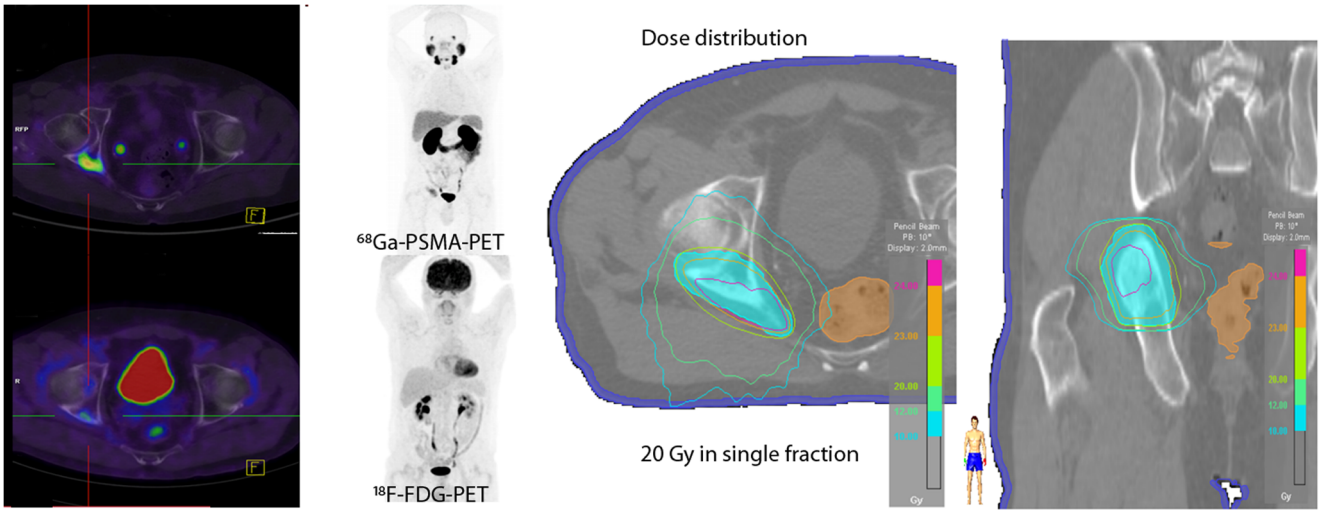

Fig. 1 Case example of PET imaging (left) and SBRT plan (right) in metachronous oligometastatic disease of 71-year-old male with elevated PSA following prior radical prostatectomy managed with 20 Gy in single fraction to single right acetabulum metastasis and androgen deprivation therapy

PET/CT has a sensitivity of 79%, specificity of 97%, and diagnostic accuracy of 84% [61]. For lymph nodes, it has a sensitivity of 33–100% and specificity of 95–100% [62].

Increasingly, PET using ^{68}Ga prostate-specific membrane antigen (PSMA), which detects for cellular expression of PSMA, is being utilized for staging prostate cancer patients. A high level of inter-observer agreement has been shown with ^{68}GaPSMA PET/CT imaging for the diagnosis of both lymph node and bone metastases [63]. A systematic review of the use of ^{68}Ga-PSMA PET in the primary setting showed variable sensitivity (range 33–99%) and specificity (> 90%), although most studies showed increased detection rates compared to traditional imaging modalities [64]. Another systematic review and meta-analysis that reported on ^{68}Ga-PSMA PET in both the primary and biochemical recurrence setting showed a summary per-lesion sensitivity and specificity of 80% and 97% respectively [65]. Interestingly, ^{68}Ga-PSMA PET was shown to have a greater detection rate in the recurrent compared to primary setting (76% vs 40% respectively). Additionally, in the recurrent setting, ^{68}Ga-PSMA PET showed greater detection with higher PSA values; however, even at PSA levels of 0–0 .2ng/mL, it showed a detection rate of 42%. The utility of ^{68}Ga-PSMA PET, particularly in the recurrent setting, is further supported by the results of a multicenter prospective study, which showed ^{68}Ga-PSMA PET resulted in a change in management intent in 21% of patients in the primary setting, and 62% of patients in the recurrent setting [66]. Limitations of PET however include difficulty in identifying very small volume disease less than 5 mm in size.

Whole-body MRI (with T1, T2, short tau inversion recovery, and diffusion weighted imaging sequences) allows for complete assessment of both bony and soft tissue disease, functional assessment of the tumor following therapy as active or dead and elimination of radiation exposure to the patient. Several meta-analyses have shown that the accuracy of MRI is superior to choline PET, CT, and bone scintigraphy in multiple cancer types on a per-patient and per-lesion basis [58, 67–69]. In prostate cancer, a meta-analysis of 27 studies showed that on a per-patient basis, the pooled sensitivities for bone disease using choline PET/CT, whole-body MRI, and bone scintigraphy were 0.91 (95% CI 0.83–0.96), 0.97 (95% CI 0.91–0.99), and 0.79 (95% CI 0.73–0.83) and pooled specificities were 0.99 (95% CI 0.93–1.00), 0.95 (95% CI 0.90–0.97), and 0.82 (95% CI 0.78–0.85), respectively [58]. Limitations of whole-body MRI however include its higher cost, restricted availability of diagnostic technique and radiologist expertise, and longer duration of the examination.

The critical need for integrating modern imaging into the design of in particular oligometastatic studies, in which outcomes are dependent upon the volume and distribution of metastatic spread, has been recognized most recently by the European Organization for Research and Treatment of Cancer (EORTC) Imaging Group, who have provided guidelines on the incorporation of modern imaging at the various stages of prostate cancer to select patients with oligometastatic disease [3]. If available outside the context of a clinical trial, utilization of PET for staging patients, particularly in the recurrent setting, may allow for improved detection of oligometastatic disease and incorporation of MDT, while whole-body MRI techniques may allow for better characterization of treatment response. With the incorporation of increasingly sensitive methods of imaging, however, the effect of upstaging patients who would have previously been classified as having node-negative or non-metastatic disease, must be considered, when interpreting and comparing results such as progression-free survival from future studies.

Future Directions

There are currently at least eight prospective phase II/III trials recruiting patients to investigate MDT in the setting of recurrent hormone-sensitive metastatic prostate cancer. Most studies are

investigating the role of SBRT in addition to ADT in patients with oligometastatic disease with or without treatment to the primary (CROP, NCT02563691; phase II Study of SBRT as Treatment for Oligometastases in Prostate Cancer, NCT02192788; Radiotherapy for Oligometastatic Prostate Cancer, NCT01859221), while one study investigates the role of IMRT in this setting (IMRT in Treating Patients Undergoing Androgen Deprivation Therapy for Metastatic Prostate Cancer, NCT00544830). MDT for CRPC is a novel area in which a few small retrospective series have been published [70], with prospective trials also now emerging to assess the additional benefit of SBRT to hormonal therapy in delaying disease progression and change in systemic therapy (PCS IX, NCT02685397 and TRAP, NCT03644303). Local therapy for patients with nodal only oligorecurrent disease is also being investigated in PEACE V STORM (NCT03569241), in which patients are randomized to receive sLND or SBRT to the nodes with or without whole pelvic radiotherapy to 45 Gy, and OLIGOPELVIS (NCT02274779), a single-arm study in which patients receive 54 Gy to the pelvis with a boost of 66 Gy to the lymph nodes in addition to ADT. The value of local treatment including radiotherapy and surgery to the prostate is also being explored in a number of ongoing early phase I/II, as well as a couple of randomized phase III trials (g-RAMPP, NCT02454543 and PEACE1, NCT01957436). In the synchronous setting, the phase III randomized SWOG 1802 trial (NCT03678025) and the randomized controlled feasibility trial, Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone (TRoMbone, ISRCTN15704862), will investigate the role of surgery to the primary [71]. The question of whether local therapy to metastatic lesions in addition to local therapy to the primary is beneficial in the setting of de novo oligometastatic disease will also be addressed by upcoming randomized trials including through arm M of the STAMPEDE trial (NCT00268476) and PLATON (NCT03784755), which will include patients with both synchronous and metachronous disease.

The combination of these trials will allow us to explore various treatment approaches in the setting of oligometastatic prostate cancer and hopefully better appreciate the risks and benefits of these approaches.

Conclusion

Oligometastatic prostate cancer is an increasingly recognized entity, in which novel imaging and therapeutic approaches present an opportunity for clinicians to gain new insights into the metastatic process, as well as potentially provide the tantalizing opportunity for cure in a previously palliative cohort of patients. While results of multiple retrospective and early phase trials suggest that select patients may be living longer with the use of MDT in addition to cytoreductive treatment, a number of ongoing prospective trials will need to report their final results for us to have a better understanding of how best to incorporate this into clinical practice that may likely shift current paradigms and guidelines.

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phase 3 trial. Lancet. 2018;392:2353–66. https://doi.org/10.1016/S0140-6736(18)32486-3**Randomized Phase III trial of ADT +/- prostate radiotherapy which showed a statistically significant overall survival benefit in patients with low volume metastatic disease**.

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