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Metastases-directed radiotherapy in castration resistant oligo metastatic prostate cancer: A multicentric retrospective study from the French group COLib

J. Chamois [a,*], A.L. Septans [b], B. Schipman [c], E. Gross [d], N. Blanchard [e], V. Passerat [f], C. Debelleix [g], C.G. Hemery [h], I. Latorzeff [i], Y. Pointreau [j]

[a] Centre Hospitalier privé, Saint Grégoire, France
[b] Statistiques, Weprom, Angers, France
[c] Radiotherapie, Institut de Cancerologie de Bourgogne, Dijon, France
[d] Radiotherapie, Hopital prive Clairval – Ramsay Sante, Marseille, France
[e] Radiotherapie, Centre de Cancerologie les Dentellieres, Valenciennes, France
[f] Radiotherapie, Orlam, Villeurbanne, France
[g] Radiotherapie, Clinique, Bordeaux Tivoli- Ducos, Bordeaux, France
[h] Radiotherapie, CHU, Reims, France
[i] Radiotherapie, Clinique Pasteur, Toulouse, France
[j] Radiotherapie, Institut Interrégional de Cancerologie, Le Mans, France

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ABSTRACT

Oligometastases are defined as a number of detectable metastases less or equal to 5. In castrate-resistant oligo metastatic prostate Cancer (CR oligoM PC), Metastases-Directed Ablative radiotherapy (MDRT) is poorly investigated. Our study retrospectively reviewed the cases of CR oligoM PC treated with MDRT in 8 French high-volume radiotherapy centers.

OS and PFS are defined as the delay between the first day of MDRT and death (OS) or progression according to PCWG criteria (PFS). OS and PFS are evaluated according to Kaplan Meyer, curves are compared with log rank test. Logistic regression was used to identify predictive factors for outcome: bone versus node metastasis, ISUP grade, PSA doubling Time (PSADT) at the time of MDRT, time to castration resistance.

107 patients were included in the study, among those 197 metastases received MDRT. For the overall population, the median follow-up was 25.2 months (1,4–145). OS was 93 % at 2 years and 81,4% at 3 years. At 2 years, 100 % of patients with node-only metastasis were alive versus 88,7% among those who have bone metastases ($p = 0,72$). The median PFS was 12,6 months (IC 95 % [9,6; 17]), with no difference among patients with node only disease versus the rest of the cohort.

The PFS was 18,2 months (10,0; 32,4) in patients with PSADT >6 months versus 10,7 months (8,9; 14,3) when PSADT was inferior to 6 months. However, this difference did not reach significant.

We did not find a correlation neither between ISUP grade (1–2 versus 3–4-5) and PFS, nor between hormone-sensitivity duration and PFS.

Patients receiving MDRT for CR oligoM PC have a good prognosis with 81,6% OS at 3 years. PSA DT longer than 6 months could be related to better PFS. MDRT strategy could postpone the onset of new systemic treatment with median PFS >1 year.

Introduction

Oligometastases are typically characterized by the presence of five or fewer detectable metastases. This concept, introduced by Hellman and Wechselbaum [1], is of growing interest for several reasons: [1] advancements in more sensitive diagnostic techniques, such as metabolic assessments, have led to the identification of a greater number of oligometastatic cases; [2] oligometastatic disease is increasingly

* Corresponding author.
E-mail addresses: jerome_chamois@yahoo.fr (J. Chamois), a.septans@ilcgroupe.fr (A.L. Septans), ilatorzeff@clinique-pasteur.com (I. Latorzeff).

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recognized as a distinct entity with unique immunologic and prognostic characteristics; [2], and [3] recent studies have either demonstrated or suggested the clinical benefits of specifically targeting oligometastases, with or without concurrent systemic therapies, across various clinical contexts. [3,4].

The benefit of ablative radiotherapy aimed at metastases in cases of hormone-sensitive oligometastatic prostate cancer has been substantiated by multiple ongoing prospective studies and is currently under investigation in ongoing randomized trials. [4,5,6] Conversely, in oligometastatic castrate-resistant prostate cancer (oligoM CRPC), the potential benefits of metastases-directed therapies, such as ablative radiotherapy, have not been as thoroughly explored. Despite this, the occurrence of oligometastases in CRPC patients is relatively common. Our investigation retrospectively examines the cases of oligoM CRPC patients who received Metastases-Directed Ablative RadioTherapy (MDRT) across eight high-volume radiotherapy centers in France, aiming to contribute to the understanding and management of this condition.

Objectives

The aim of this study was to delineate the characteristics and outcomes of patients undergoing metastasis-directed radiotherapy (MDRT) within the context of oligometastatic castration-resistant prostate cancer (OligoM CRPC).

Materials and methods

Eligibility for inclusion in our study required patients to have oligometastatic castration-resistant prostate cancer (CRPC) and to undergo metastasis-directed radiotherapy (MDRT). The criteria for defining oligometastatic CRPC included:

- Histologically confirmed prostate cancer (PC).
- Evidence of castration resistance, defined by disease progression despite a testosterone level below 50 ng/mL.
- Five or fewer detectable metastases using prostate cancer-specific metabolic imaging. Given the superior sensitivity of prostate cancer-specific imaging compared to traditional modalities (bone scan and CT scan), assessment of oligometastatic disease was based on metabolic imaging techniques such as 18 Fluoro choline PET scan or PSMA PET scan [7]. Metabolic work-up was mandatory, as research on “non-metastatic CRPC” has revealed that up to 75 % of these patients exhibit detectable relapses, predominantly in lymph nodes or bones, when assessed with PSMA PET or Fluciclovine PET. [8,9].

MDRT was specified as radiation therapy (RT) aimed at definitively treating identified metastases. RT could be administered following a normofractionated regimen (2 Gy/session up to a minimum of 60 Gy) or a hypofractionated regimen utilizing stereotactic body radiation therapy (SBRT). Only therapeutic, not palliative, RT was considered. All identified targets were required to undergo MDRT.

This retrospective study reviewed the medical records of patients treated with MDRT for OligoM CRPC across 8 French cancer treatment centers participating in the COLIB initiative. Patient inclusion required meeting all of the criteria mentioned above. RT utilization was confirmed by a multidisciplinary Tumor Board.

The study was conducted in accordance to the ethical standards of the institutional committee and the 1964 Helsinki declaration and its later amendments. The study complies with the reference methodology adopted by the French Data Protection Authority (CNIL) and patients, or their proxies, were informed about the study in writing and provided no objections to the use of their clinical data for the research purposes.

Data collected for each patient included demographic and clinical information (age at diagnosis and at the time of MDRT), ISUP Group at PC diagnosis, duration of the hormone-sensitive phase, treatments during the hormone-sensitive phase, dates of metastasis detection and castration resistance onset, and oligometastasis characteristics (number and type: bone or lymph node). Treatment details (date, total and per session doses, fractionation scheme) were also recorded. For each patient, PSA doubling time was calculated at the time of MDRT using the formula: $\ln(2) \times T/(\ln \text{post-MDRT PSA} - \ln \text{pre-MDRT PSA})$, with PSA levels measured within three months before and after MDRT.

Patients were divided into two categories based on the timing of oligometastasis detection: 1) during the hormone-sensitive phase, later developing castration resistance; 2) at the onset of castration resistance. Further analysis distinguished between three groups based on treatment: i) Group A, those who received MDRT and new castration-resistance specific treatment (CRST); ii) Group B, those treated with MDRT alone, without CRST; and iii) Group C, patients treated with MDRT for oligometastases resistant to Androgen Receptor Targeting Agents (ARTA). The PSA response, defined as the rate of change in PSA levels from pre-MDRT to post-MDRT nadir, was evaluated for each group.

Statistics

Primary endpoint

The primary endpoint of this study was Progression-Free Survival (PFS), which we defined as the duration from the initial day of radiotherapy to the occurrence of disease progression. Disease progression was determined by either of the following criteria: [1] a biological increase in Prostate-Specific Antigen (PSA) exceeding 25 % of the PSA level recorded at the commencement of radiotherapy, with a PSA value greater than 2 ng/mL, as specified by the Prostate Cancer Working Group 3 (PCWG3); or [2] radiological evidence of progression, indicated by the emergence of more than one new lesion.

Secondary endpoints

The study also evaluated:

- Time to New Systemic Treatment: Defined as the period from the first session of radiotherapy to the initiation of any new systemic therapy. Notably, a subsequent course of radiotherapy did not qualify as a new systemic treatment.
- Overall Survival (OS): This metric was assessed alongside PFS.

Statistical analysis

Progression-Free Survival (PFS) and Overall Survival (OS) were estimated using the Kaplan-Meier method. To identify factors predictive of PFS, logistic regression analysis was employed. All statistical analyses were conducted using SAS software, version 9.4.

Results

This study included 107 patients, from which 197 metastases were treated with metastases directed radiotherapy radiotherapy (MDRT). The number of metastases treated per patient ranged from 1 to 4, with a median of 2. Thirteen patients underwent a second course of MDRT due to new oligoprogression events, none of which occurred in previously treated volumes.

The median age at prostate cancer (PC) diagnosis was 65 years (range: 44–85 years), increasing to 73 years (range: 50–94 years) at the time of MDRT administration. 91 % of the cohort received primary tumor management through surgery, external beam radiation therapy, or brachytherapy. During the hormone-sensitive phase, metastases were detectable in 52 % of the patients, though MDRT was administered upon progression to castration-resistant phase, with the remaining 48 %

presenting detectable metastases at this latter phase. The average duration of hormone sensitivity in the cohort was 31.8 months (range: 3.8–225 months). ISUP grading, based on initial biopsy cores or prostatectomy specimens, was distributed as follows: Grade 1 in 13 patients, Grade 2 in 26, Grade 3 in 24, Grade 4 in 23, Grade 5 in 16, with 5 patients having an unknown grade.

For the hormone-sensitive metastatic phase, treatment included LHRH agonists or antagonists for all patients, complemented by abiraterone (2 %), Docetaxel (5 %), or peripheral steroid antiandrogens (6 %). It is important to note that the majority received their hormone-sensitive phase treatment prior to the introduction of new androgen receptor-targeting agents, now the standard of care for hormone-sensitive metastatic disease. Among patients who developed metastases during the castration-resistant phase, treatment protocols included LHRH agonist or antagonist alone (40 %), abiraterone or enzalutamide (52 %), bicalutamide (2 %), docetaxel (3 %), with 3 % of treatments undocumented.

Metastatic distribution was as follows: 54.2 % had bone-only metastases, 37.4 % had node-only metastases, 7.5 % presented with both bone and nodal metastases, and a single patient (0.9 %) had a lung metastasis. The prostate-specific antigen (PSA) doubling time (PSADT) at the initiation of MDRT was less than 6 months in 80 patients, while only 13 patients exhibited a PSADT longer than 9 months.

Patient characteristics are summarized in Table 1. Regarding MDRT dosing, the median total dose to nodal metastases was 36 Gy (range: 21–45 Gy) with a median dose per session of 6 Gy (range: 5–9 Gy). For bone metastases, the median total dose was 27 Gy (range: 18–45 Gy) with a median dose per session of 9 Gy (range: 5–10 Gy). A subgroup of patients received a normofractionated regimen delivering 62 Gy to nodal metastases.

Across the entire cohort, the median follow-up duration was 25.2 months (range: 1.4–145 months). The overall survival rates were 93 % at 2 years and 81.4 % at 3 years. The 2-year OS rate was 100 % for patients with node-only metastases compared to 88.7 % for those with bone metastases ($p = 0.72$). The median PFS was 12.6 months (95 % CI [9.6; 17]), with no significant difference observed between patients with node-only disease and the broader cohort (Figs. 1 and 2). The PFS for patients with a PSADT greater than 6 months was 18.2 months (10.0; 32.4), compared to 10.7 months (8.9; 14.3) for those with a PSADT of less than 6 months, although this difference was not statistically significant. Fig. 3.

Notably, within our patient cohort, the PSADT was generally short, with a minimal number of individuals having a PSADT longer than 9 months, indicating a relatively rapid disease progression in most cases.

No correlation was found between ISUP grade (1–2 vs. 3–4-5) and PFS, nor between hormone sensitivity duration and PFS. The average time to new systemic therapy from the start of MDRT was 16.9 months (±13.2 months), with a median time of 12.4 months (range: 3.3–57.8 months).

Fifty-one patients manifested detectable metastases upon reaching castration resistance. These patients were stratified into three groups for analysis: Group A included patients who received MDRT and new castration-resistance specific treatments (CRST); Group B consisted of patients who received MDRT without CRST; and Group C encompassed patients treated with MDRT for ARTA-resistant oligometastases. The PSA response rates (PSA50) were 83.4 % in Group A, 31 % in Group B, and 20 % in Group C. Fig. 4 Notably, PSA progression within 3 months post-MDRT was observed only in Groups B and C. The three-year OS rates were 84 %, 87 %, and 44 % for Groups A, B, and C, respectively, as detailed in Table 2.

Discussion

To date, this series represents the largest collection of multidisciplinary treatment response (MDRT) in oligometastatic castration-resistant populations ever published. The survival outcomes at two

Table 1
Patients characteristics.

Nb of patients	107
Nb of metastases treated by MDRT	197
Age at diagnosis (years)	**65 [44; 85]**
Age at MDRT (years)	**73 [50; 94]**
ISUP group at diagnosis	ISUP 1: 13 (12,1%)ISUP 2:26 (24,3%)ISUP 3:24 (22,4%)ISUP 4: 23 (21,5%)ISUP 5: 16 (15 %)Unknown:5 (4,7%)
Treatment of the primary tumor	No treatment: 10 (9,3%) Prostatectomy:47 (44 %)Radiotherapy:46 (43 %)Brachytherapy:1 (0,9%)Unknown:3 (2,8%)
Duration of hormono-sensitivity (median, months)	38.1 [3.8; 225.6]
PSA doubling time at MDRT	≤6 months: 80 6–9 months: 10 >9 months: 13 Unknown: 4
Metastasis type (nb patients)	Bone and node: 8 (7,5%) Bone-only: 58 (54,2%)Node-only: 40 (37,4%)Lung: 1 (0,9%)
detection of metastasis:	
hormonosensitive phase:	**56 (52 %)**
-Synchronous/hormonosensitive	39
-Metachrounous/hormonosentitive	17
At castration resistance	**51 (48 %)**
Metabolic imaging used	107 (100 %) 86
^{18}F Choline TEP	(80,4%)21
PSMA TEP	(19,6%)
Systemic treatment at hormonosensitivity phase:	93
LHRH agonist or antagonist	(86,9%)7
LHRH agonist + bicalutamide	(6,5%)2
LHRH agonist + abiraterone	(1,9%)5
LHRH agonist + docetaxel	(4,7%)
Radiotherapy of oligometastases:	
Number of treatments	**197 (100 %)**
Hypofractionated SBRT on node metastases-median total dose	**45 (22,8%)**
(Gy)-median dose/fraction	36 [21; 45]
(Gy)	6.0 [5;9]
Hypofractionated SBRT on bone metastases-median total dose	**93 (47,2%)**
(Gy)-median dose/fraction	27 [18; 45]
(Gy)	9,0 [5;10]
Normofractionation 2 Gy/fraction (on node metastases only)-median total dose	**59 (30 %)**
(Gy)	62 [54;70]
Patients developing metastases at castration resistance:	**51**
-group A: MDRT + castrate Resistance specific Treatment (CRST)	12
-group B: MDRT only	29
-group C: MDRT at CRST resistance	10

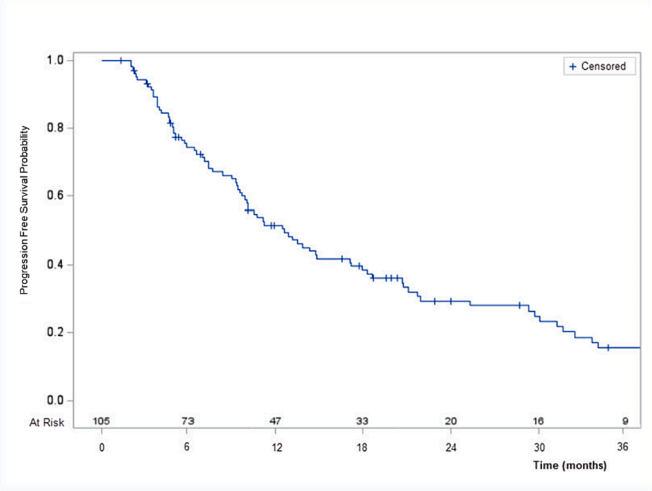

Fig. 1. Progression Free Survival.

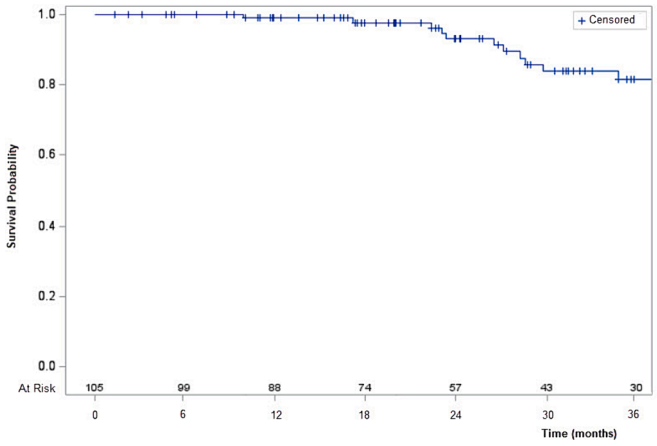

Fig. 2. Overall Survival.

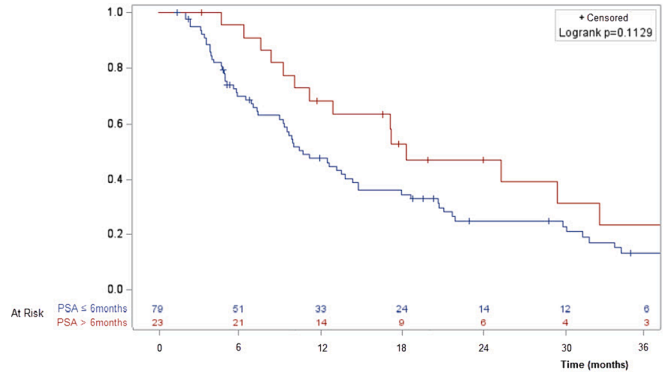

Fig. 3. Progression free survival according to PSA Doubling Time. Blue curve: PSA ≤6 months; red curve PSA >6 months. P 0.11. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and three years—93 % and 81.4 %, respectively—are notably superior when juxtaposed with the overall survival figures detailed in the COU AA 302 or PREVAIL trials. [10,11] However, it's critical to acknowledge the distinct nature of our cohort, characterized by a less extensive metastatic burden. This distinction reinforces the prognostic advantage associated with oligometastatic states, even within the domain of

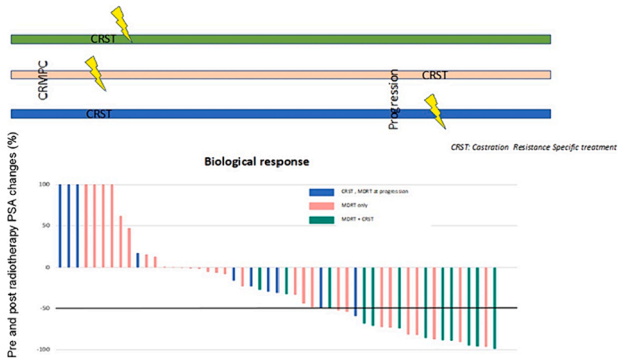

Fig. 4. We divided the population of patients developing detectable metastases at the time of castration resistance in 3 groups: group A, patients who received MDRT AND new Castration-Resistance Specific Treatment (CRST)(green group), group B who received MDRT WITHOUT CRST (pink group), and group C: those who received MDRT for CRST resistant disease (blue group). PSA variation is the change rate between pre MDRT PSA value and post MDRT PSA nadir. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Overall survival and Progression free survival in three groups MDRT + CRST, MDRT without CRST and MDRT at ARTA resistance.

Overall Survival			
Variable	Results		
	MDRT Only	CRST + MDRT	CRST+/MDRT at progression
N	29	12	10
N with event	6	1	2
Censored	23	11	8
Median OS	NA	NA	28,2 [9,8;NA]
3 years OS	84.10 %	87.50 %	43.70 %
IC95%	[57,7; 94,7]	[38,7; 98,1]	[1,0; 86,0]
p-value		0.1065	
Progression Free Survival			
Variable	Results		
	MDRT Only	CRST + MDRT	CRST+/MDRT at progression
N	29	12	10
N with event	23	8	7
Censored	6	4	3
Median PFS	14.7	21	5.5
IC95%	[8,3; 25,3]	[9,2; 49,5]	[2,4; NA]
p-value		0.426	

MDRT: metastases Directed Radiotherapy; SBRT Stereotactic Body radiotherapy; CRST Castrate Resistance Systemic Treatment.

castration-resistant prostate cancer. Our median progression-free survival (PFS) stands at 12.6 months, a figure that aligns with the optimistic prognosis highlighted by Triggiani across a significant cohort of 86 patients and 117 metastases, each treated with MDRT for oligometastatic CRPC, revealing a new-metastasis-free survival of 12 months (95 % CI [5; 19]) and PFS rates of 52 % and 33 % at the two and three-year benchmarks, respectively. [12] In a recent study involving 141 oligometastases identified through PET PSMA imaging in 42 patients, the reported median progression-free survival (PFS) was 12 months. [13] This finding is notably similar to the 33 % two-year PFS rate observed in our research. Such a comparison aligns closely with results from Onal and colleagues, who documented a two-year PFS of 34 % in a cohort of 67 patients undergoing MDRT for 133 metastases, of which 64 % were bone metastases. This parallel underscores the consistency of PFS outcomes across studies focusing on oligometastatic CRPC treated with MDRT, particularly highlighting the prevalence and impact of bone metastases within these patient groups. [14].

In our investigation, we noted a 2-year overall survival (OS) of 100 %

for patients with nodal-only relapse, compared to an 88.7 % 2-year OS for those with bone or both bone and nodal relapse. Although this difference did not reach statistical significance, this observation is in line with findings from Yoshida, who reported in a smaller series of 23 oligometastatic CRPC patients treated for bone oligometastases (15 patients) or nodal pelvic relapse (7 patients), that the time to progression was notably different—10 months for nodal MDRT versus 4.8 months for bone MDRT. This suggests that patients with nodal relapses might have a better prognosis. [15].

In the study conducted by Pezzulla et al., 38 patients with a total of 61 oligoprogressive castration-resistant nodal metastases treated with stereotactic body radiotherapy (SBRT) were reported to have a two-year progression-free survival (PFS) rate of 47 % and an outstanding two-year overall survival rate of 90 %. Remarkably, two-thirds of the patients in this cohort did not require the initiation of new systemic treatments within a two-year timeframe. [20] This outcome reinforces the findings from our own study, which similarly highlights the favorable prognosis for patients undergoing ablative treatments specifically targeting nodal recurrences in the context of castration-resistant prostate cancer. Our data further support the effectiveness of such targeted ablative approaches in managing this patient subgroup.

The majority of our patient cohort underwent treatment prior to the publication of findings from the SPARTAN, ARAMIS, and PROSPER trials. These pivotal studies highlighted the efficacy of the next-generation hormonal therapies—apalutamide, darolutamide, and enzalutamide, respectively—in managing non metastatic castration-resistant prostate cancer (CRPC) with a PSA doubling time (DT) of less than 9 months. This specific PSA DT threshold was selected based on its association with a significantly increased risk of developing detectable metastases within the subsequent 12 months. The trials collectively demonstrated improvements in both progression-free survival (PFS) and overall survival (OS), establishing these next-generation hormonal therapies as the new standard of care for CRPC patients experiencing a biological relapse with a short PSA DT. Prior to these developments, the conventional approach entailed watchful waiting alongside continuous androgen deprivation therapy until the emergence of metastases. The potential for metastasis-directed radiotherapy (MDRT) to enhance outcomes in patients with oligometastatic disease—those detectable only through high-sensitivity metabolic imaging techniques like Fluciclovine PET, 18F Choline PET, or PSMA PET—within the context of treatment with new-generation antiandrogens remains unproven. Nonetheless, several retrospective studies have begun to explore this possibility, offering insights that warrant further discussion.

Within the context of castration-resistant prostate cancer (CRPC), there remains a lack of consensus regarding the optimal care pathway for patients experiencing a rise in PSA levels alongside a prolonged PSA doubling time (PSADT) greater than 9 months, especially when their oligometastatic disease cannot be detected via bone scans. Notably, 31 % of patients who underwent MDRT exclusively (absence of any Androgen Receptor Targeting Agent (ARTA)) witnessed a PSA reduction of over 50 % alongside an impressive 2-year overall survival (OS) rate of 87 %. This outcome suggests that MDRT has the potential to either postpone the need for ARTA initiation or extend the interval before necessitating treatment adjustments in certain patient cohorts. Specifically, among 68 patients who received MDRT for oligometastases without the incorporation of any specific systemic agents for the castration resistance phase, the median duration until the requirement for new systemic treatment emerged was 12 months. In contrast, the Triggiani series reported a median timeframe to the initiation of new systemic therapy as extended as 21 months. [12] It is important to note, however, that two-thirds of the participants in Triggiani's study presented with solely nodal relapse, whereas only one-third had bone metastases. Similarly, Onal's research indicated that the employment of an MDRT strategy successfully deferred the introduction of new systemic treatments for up to two years in 67 % of cases. [14] Nonetheless, caution must be exercised when interpreting these delays in the context of new systemic treatment initiation, given that the criteria for prescribing new treatments are not consistently detailed across various studies and are frequently left unspecified.

How can we improve patient selection for this therapeutic strategy?

There is no definitive evidence highlighting a benefit of MDRT in oligoM CRPC. Retrospective studies that have hinted at a potential advantage have examined various factors, such as PSA response, time to progression, and overall survival (OS), to identify any correlations that might inform better patient selection.

In our analysis, the progression-free survival (PFS) extended to 18.2 months (range 10.0 to 32.4 months) for patients with a PSA doubling time (PSADT) greater than 6 months, compared to a PFS of 10.7 months (range 8.9 to 14.3 months) for those with a PSADT less than 6 months. Despite the numerical difference, this variance was not statistically significant. It's noteworthy to mention that the overall cohort exhibited a relatively short PSADT, with a small fraction of patients having a PSADT longer than 9 months. This cohort represents the inaugural analysis to evaluate the impact of PSA doubling time at the point of MDRT decision-making on patient outcomes. Furthermore, our study identified no significant correlation between the International Society of Urological Pathology (ISUP) grade at diagnosis, the duration of the hormone-sensitivity phase, the PSA level at the start of MDRT, and the subsequent progression-free survival. This observation does not align with suggestions from Mai's cohort that patients who experience a brief hormone-sensitive phase may derive less benefit from cytoreductive radiotherapy during the castration-resistant phase of their disease [22]. However, only 28 % of patients had oligometastatic disease in this cohort.

In the retrospective study conducted by Valeriani, an analysis revealed that patients who were treated with abiraterone in combination with metastasis-directed radiotherapy (MDRT) exhibited superior outcomes if they had been on abiraterone therapy for more than six months prior to undergoing MDRT. Specifically, the progression-free survival (PFS) post-MDRT in this subgroup was 27 months, compared to 18 months observed in the general study population. [16] Similarly, an evaluation of a cohort comprising 67 patients with castration-resistant metastatic prostate cancer (CRmPC), who were treated with either enzalutamide or abiraterone, indicated that those who had received androgen receptor targeting agents (ARTAs) for a duration exceeding six months experienced a longer PFS from MDRT, with figures of 9.5 months versus 5 months for those treated for shorter durations. [17]. It's important to underscore, however, that the length of time a patient remains responsive to new androgen-targeting agents is a prognostic factor in its own right. Consequently, the extended duration of hormone therapy should not be solely relied upon as a criterion for selecting patients for the MDRT approach.

In our study, we closely examined 10 patients who underwent MDRT for progressive oligometastases while being treated with androgen receptor targeting agents (ARTAs). Among these, only two patients exhibited a 50 % reduction in PSA levels, four experienced a PSA decrease of less than 50 %, and the remaining four encountered an immediate increase in PSA following MDRT, leading to a median progression-free survival (PFS) of 5.5 months in this subgroup. This contrasts with findings from Onal et al., who in their series on 54 patients treated with MDRT for oligoprogressive disease under abiraterone or enzalutamide, reported that 22 % had an immediate increase in PSA, whereas 61 % achieved a PSA response greater than 50 %. [18].

In a practical clinical setting, Detti's study involving 32 patients demonstrated that radiotherapy targeting oligoprogressive sites resistant to abiraterone extended the median PFS to 9.6 months, suggesting a potential to prolong the efficacy of abiraterone and delay the need for new systemic therapies. [21] However, the criteria for selecting patients for MDRT in the context of progressive disease under new hormonal therapies remain to be clarified.

Our analysis also included 12 patients receiving concurrent new antiandrogen therapies and MDRT upon detection of their castration-

resistant (CR) oligometastases. In this group, the median symptomatic skeletal event-free survival (SSP) was 21 months, with no patients experiencing a PSA increase post-treatment. Remarkably, 83 % (10 out of 12) of these patients achieved a 50 % PSA response, highlighting the effectiveness of combining MDRT with new anti-androgen treatments.

The question of whether adding MDRT to abiraterone enhances outcomes for CR oligometastatic prostate cancer was prospectively investigated by Francolini et al. through the ARTO study, a multicentric phase II randomized trial. This study allocated 157 patients with oligometastatic CRPC to either a control arm receiving abiraterone alone or an experimental arm receiving both abiraterone and MDRT for detectable metastases. The experimental arm achieved the primary objective, exhibiting a biological response rate of 92 % compared to 68 % in the control arm, with an odds ratio (OR) of 5.3 (95 % CI 2–13; $p = 0.001$). Additionally, an improvement in PFS was observed, further supporting the integration of MDRT in the treatment regimen for this patient population [19].

In our analysis of 29 patients who were treated with MDRT while continuing their existing hormone therapy regimen, without the addition of new therapeutic agents, we observed a median progression-free survival (PFS) of 14.7 months and an overall survival (OS) rate of 84 % at three years. This outcome suggests the possibility of deferring new treatment interventions without adversely affecting patient prognosis. However, such a conclusion cannot be drawn from a retrospective study. A careful monitoring is recommended in this approach, as evidenced by a 27.5 % increase in PSA levels within three months post-radiotherapy in 8 of these 29 patients. Additionally, a PSA response of 50 % was seen in 34 % of the patients. Complementarily, Onal and colleagues, in their study involving 133 metastases treated with an MDRT approach in 67 patients who did not receive any new systemic hormone therapies, reported a 2-year PFS of 34.4 %. Notably, two-thirds of these patients had not commenced androgen receptor targeting agents (ARTAs) by the two-year mark. [14] These findings are in alignment with our results, underscoring the potential of MDRT to delay the initiation of new treatments and highlighting the need for further research to refine patient selection for this treatment strategy.

The findings and methodologies applied in selected series that explore the use of MDRT in both oligometastatic CRPC and oligoprogressive CRPC scenarios are concisely summarized in Table 3. This table serves as a reference point for comparing the outcomes and approaches across different studies, facilitating a deeper understanding of the role of MDRT in managing these complex cases.

Conclusion

Castration-resistant oligometastatic prostate cancer represents a distinct clinical category within prostate cancer management. In our study of metastasis-directed radiotherapy, interesting clinical outcomes suggest that this strategy could postpone the necessity for initiating new systemic therapies by an average of 12 months. These findings align with those from several smaller studies previously published and need to be prospectively evaluated. The debate continues as to whether MDRT should be employed solely to defer the introduction of new systemic agents or if it should be incorporated alongside androgen receptor targeting agents (ARTAs) as part of a more aggressive treatment strategy. The necessity for a rigorous evaluation of these strategies through prospective, randomized clinical trials is evident.

The ongoing clinical trial NCT03503344 is particularly noteworthy, as it seeks to compare two different approaches in patients with castration-resistant oligometastatic prostate cancer: one arm receiving enzalutamide alone for one year, and the other combining enzalutamide for one year with metastasis-directed stereotactic body radiotherapy (SBRT) [23]. The trial's primary outcome is the proportion of patients achieving an undetectable PSA level six months following the completion of enzalutamide treatment. Similarly, the NCT04319783 study is investigating the efficacy of combining darolutamide with metastasis-directed SBRT in patients with castration-resistant metastatic prostate cancer. Should these studies yield positive results, they will support the rationale for an upfront treatment intensification in oligometastatic CRPC that integrates ARTA with MDRT. Such an approach could not

Table 3
Available series addressing MDRT in oligoM CRPC and oligoprogressive CRPC.

Series	Type	N patients	N metatstes	Progression free survival	Others findings
Trigiani [12]	retrospective	86	117 2/3 node 1/3 bone	52 % at 2 years 33 % at 3 years	Time to next treatement: 21 months
Onal [14]	retrospective	67	133	34 % at 2 years	Freedom from new treatment: 67 % at 2 years
Yoshida [15]	retrospective	23	15 bone 7 pelvic node		Time to progression: 4,8 months (bone) Time to progression: 10 months (node)
Henkenberens [13]	retrospective	42	141	12 months	
Pezzulla [20]	retrospective	38	61 node only	47 % at 2 years	OS: 90 % at 2 years Freedom from new systemic treatment: 66 % at 2 years
Series adressing specifically MDRT in oligoprogressive disease in CRMPC patients receving ARTAs					
Valeriani [16]	retrospective	29	37	18,4 months	Overall duration ARTA: 14,8 months Longer PFS when progression occured <6 months after ARTA initiation
Massaro [17]	retrospective	42	67	19,8 months	Median OS: 32,5 months 2 years OS: 64 % MDRT occured <6 months ARTA: OS 23,4 months MDRT occured >6 mounths ARTA: OS 45 mounths
Onal [18]	retrospective	54	126	17 months	Time to new treatment: 8,6 months ARTA duration before progression <6 months as predictor of worse outcome
Detti [21]	retrospective	32		9,6 months	
Francolini [19] ARTO	Phase II prospective trials: Abiraterone vs Abiraterone + SBRT	157			Primary endpoint biological response Abiraterone only: 68 % Abiraterone + SBRT: 92 %

OS: Overall Survival; MDRT: Metastases Directed RadioTherapy; CRMPC: Castration Resistant Metastatic Prostate Cancer; ARTA: Androgen Receptor Targeting Agent; SBRT: Stereotactic Body RadioTherapy.
Event: progression as defined [1] biological progression of PSA >25 % of PSA value at the time of the start of radiotherapy and PSA >2 ng/mL as defined by PCWG3; and/or [2] radiological progression with >1 new lesion.

only enhance patient outcomes but might also offer the possibility of intermittent systemic therapy breaks for select patients, thereby potentially improving quality of life and treatment tolerability.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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