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# Radiation therapy with curative intention in men with *de novo* metastatic prostate carcinoma: shoot'em all!

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## ABSTRACT

**Background:** About 5% of prostate cancer cases are metastatic at diagnoses. Radiotherapy of both primary tumor and secondary lesions can be, in addition to systemic treatments, a radical alternative for selected patients.

**Materials and methods:** Patients with de novo prostate carcinoma with bone or lymph node metastases were retrospectively reviewed. All patients received moderate hypofractionated IMRT/VMAT up to 63 Gy in 21 daily fractions of 3 Gy to prostate and metastases with neoadjuvant and concurrent androgen deprivation therapy (ADT). According to known advances some patients also received abiraterone, enzalutamide, or docetaxel.

**Results:** Between 2015–2020, we attended 26 prostate cancer patients (median age 69.5 years, range 52–84) with simultaneous oligometastases [mean 2.1 metastases, median 1.5 metastases (range 1–6)]. Eighteen patients (69%) presented lymph node metastases, 4 (15.5%) bone metastases and 4 (15.5%) both lymph node and bone metastases. With a median follow-up of 15.5 months (range 3–65 months), 16 patients (62%) are alive and tumor free while 10 (38%) are alive with tumor. Four patients (17%) developed tumor progression, out of irradiated area in all cases, with a median time to progression of 43.5 months (range 27–56 months). Actuarial progression-free survival (PFS) rates at 12 and 24 months were 94.1% and 84.7%, respectively. No grade > 2 acute or late complications were recorded.

**Conclusions:** Simultaneous directed radical hypofractionated radiation therapy for prostate and metastases is feasible, well tolerated and achieves an acceptable PFS rate. However, further studies with longer follow-up are necessary to definitively address these observations.

**Key words:** prostate cancer; de novo oligometastes; hypofractionated radiotherapy; metastases-directed therapy

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## Introduction

Prostate cancer is the fourth most commonly diagnosed cancer in the world as well as the second most commonly occurring cancer in men with 1,276,106 new cases in 2018 representing 7.1% of all newly diagnosed cancer cases [1].

The widespread population screening through the determination of prostate-specific androgen (PSA) levels in the male population has led to

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a constant increase in the number of diagnoses of early-stage prostate cancer and a reduction in patients with de novo metastatic prostate cancer, which is assumed, according to the findings of the large PSA European Randomized Study of Screening for Prostate Cancer (ERSPC) trial, to be less than 5% of the total of newly diagnosed cases [2].

Although the presence of de novo metastasis presumes a more advanced stage of cancer, and a worse prognosis compared to the development of metachronous metastases, in the last decades the concept of oligometastatic disease has strongly emerged [3]. Defined for the first time in 1995 by Hellman and Weichselbaum as an intermediate stage between exclusively local and widely disseminated disease [4], the oligometastatic state is characterized by the presence of a limited number of metastases (≤ 5 metastases) in a limited number of organs. Those patients could benefit in terms of survival of aggressive local treatments of the oligometastatic disease. Advances in diagnostic imaging techniques, with the generalization of the use of MRl or PET-CT with tracers with greater specificity for prostate cancer such as choline, fluciclovine and the prostate-specific membrane antigen (PSMA) cause an increase in the diagnosis of oligometastatic disease from the first moment of diagnosis, favoring the adoption of specifically targeted treatments [5].

Systemic treatment with androgen blockade, sometimes combined with chemotherapy based on docetaxel, has been traditionally considered the gold standard in de novo metastatic prostate cancer. However, the increase in the diagnosis of patients with limited oligometastatic involvement leads to an increasing shift towards a more aggressive treatment and considering the option of performing a curative therapeutic approach to local disease and oligometastases [6].

The objective of our analysis in this paper is to retrospectively review our experience regarding efficacy and tolerance of a curative approach to de novo oligometastatic prostate cancer by using radiotherapy on the primary location of the tumor and on oligometases limited to patients with locoregional lymph node disease and / or extra-pelvic lymph node or bone metastases.

## Materials and methods

We have retrospectively reviewed and analyzed all the patients who were treated in our department between January 2015 and August 2020 with the diagnosis of de novo oligometastatic prostate adenocarcinoma. Inclusion criteria comprised locoregional or distant lymph node metastases and/or bone metastases without any other limitation in the number beyond the possibility of performing radiation therapy with radical intention on the primitive tumor and metastatic sites. We limited the analysis to patients with lymph node and / or bone metastases as proposed in other clinical trials included in the discussion and excluded the presence of simultaneous visceral metastases without limiting the radical intention to treat the prostate and metastases-directed therapy (MDT) by the number of metastatic sites provided that the patients' conditions and treatment characteristics allowed it. Diagnosis of metastatic involvement outside the prostate was made mostly using positron emission tomography (PET) with choline as a tracer, pelvic magnetic resonance imaging (MRI), computerized tomography (CT) or bone scan, in order of frequency.

### Radiation therapy

All included patients were treated with a moderate hypofractionated radiotherapy schedule comprising 21 daily fractions of 3 Gy up to a total dose of 63 Gy over 4.2 weeks (EQD2Gy for a/b = 1.5 of 81 Gy) on the prostate and metastatic sites concurrently with whole pelvic nodal irradiation in 21 fractions of 2.2 Gy up to 46.2 Gy (EQD2Gy for a/b = 1.5 of 48.8 Gy).

The patients were immobilized in a supine position using knee and heel supports. The patients' previous preparation for the planning CT included fasting for at least 8 hours prior to the administration of intravenous contrast, use of prior laxatives for rectal emptying and comfortably full bladder with bladder contrast. Axial images were obtained at 3 mm intervals through the prostate with a helical scanner. A CTV_p (CTV prostate) was defined as the entire prostate, seminal vesicles and areas suspected of harboring extra-prostatic extension of the tumor. A non-uniform PTV_p (PTV prostate) was created by expanding the CTV_p by 5 mm in all directions, except the posterior aspect where it was expanded by only 3 mm with the intention of reducing the risk of irradiation of the anterior wall of the rectum. A CTV_en (CTV elective nodes) including pelvic lymph nodes was defined in all patientsfrom the bifurcation of the iliac vessels and

following their trajectory by adding a 7 mm margin to encompass the distal common iliac nodes, presacral lymph nodes (S1–S3), external iliac lymph nodes, internal iliac lymph nodes, and obturator lymph node, excluding areas of overlapping with the bowel, bladder or bone. A margin of 5 mm was added to CTV_en to create PTV_en (PTV elective nodes) of pelvic lymph nodes. The definition of the areas of lymph node or bone oligometastasis was performed by fusion of the planning CT with the diagnostic PET-Choline or MR images. A third, or successive, CTV were created for the oligometastatic lesions (CTV_om) by adding 5 mm to make the corresponding PTV for oligometastatic lesions (PTV_om). The bladder, rectum, small bowel, cauda equine, femoral heads and penile bulb were contoured as organs at risk (OAR) in all patients. RayStation (RaySearch Laboratories, Stockholm, Sweden) planning treatment system was used to generate dynamic multileaf collimator plans. All patients were treated with highly conformal radiotherapy techniques, either through the use of multiple fields conformed with the intensity modulated radiotherapy (IMRT) technique or with multiple coplanar arches with the volumetric modulated arc therapy (VMAT) technique indistinctly and at the discretion of a medical physicist. Treatment planning goals and dosimetric constraints are detailed in Table 1.

Patients were treated 5 days per week. Daily verification by using LINAC cone-beam CT was performed together with Catalyst SIGRT (Surface image guided radiotherapy system of C-Rad, Stockholm, Sweden) for intrafraction patient motion management or Clarity-4D Monitoring system (Elekta AB, Stockholm, Sweden) for advanced intra-fraction motion management of the prostate and surrounding OAR. All patients were premedicated with alpha-adrenergic antagonists from the time of the planning CT scan, during radiotherapy and for at least one month after the end of the irradiation.

**Table 1.** Treatment planning and dosimetric constraints objectives and achieved results

| Structure | Criteria | Objective |
|---|---|---|
| PTVp/PTVom | V95 | > 95% (59.85 Gy) |
| | D95 | > 95% |
| PTVen | V95 | > 95% (43.89 Gy) |
| | D95 | > 95% |
| Bladder | Dmean | < 42.6 Gy |
| | V64 | < 15% |
| | V62 | < 25% |
| | V58 | < 30% |
| | V45.5 | < 50% |
| Rectum | Dmean | < 42.6 Gy |
| | V64 | < 10% |
| | V62 | < 15% |
| | V58 | < 20% |
| | V38.5 | < 60% |
| Small bowel | Dmax | < 49.4 Gy |
| | V45 | < 25% |
| Femoral heads | V42.6 | < 10% |
| Cauda equina | Dmax | < 53 Gy |
| Penilebulb | Dmean | < 42.6 Gy |

PTVp/PTVom/PTVen — planning target volumen prostate/oligometastases/elective nodal

## Hormonal and systemic therapy

All patients underwent complete hormonal blockade using antiandrogens and gonadotropin-releasing hormone (GnRH) analogues. Patients received neoadjuvant and concurrent irradiation androgen deprivation therapy (ADT) and maintained later until a minimum of 24 months or until progression of the disease, according to the preferences of the treating physician. Depending on the evolution of the clinical trials throughout the study period, treatments with docetaxel or abiraterone and prednisone were also authorized following a multidisciplinary decision of the Tumor Board.

## Evaluation and statistics

Follow-up length was estimated from the moment of initiation of first treatment (systemic treatments or radiotherapy), until the date of death or last follow-up. Evaluation of patient status was made according to clinical exams and available image tests, including CT, bone scintigraphy, MRI, PET choline. Local control (LC) was defined as the absence of relapse or evident progression in the irradiated volumes, both in the primary prostate and in the treated oligometastases. Distant metastasis-free survival (DMFS) was defined by the absence of new metastatic sites different from those initially treated. Finally, progression-free survival (PFS) was defined as the period free of local failure and/or the appearance of new distant metastases. Biochemical relapse-free survival (bRFS) was not

considered an assessable item since it could be influenced by ADT in all patients.

The Kaplan-Meier statistical analysis was used for the actuarial calculations using the log-rank test for the comparisons made between the survival curves and the Chi-square analysis for all those comparisons made between groups and statistical significance was considered to be obtained when reaching $p < 0.05$. The SPSS [IBM SPSS Statistics for Windows, Version 19.0. (Armonk, NY: IBM Corp.)] package software was used for all calculations.

The CTCAE v5.0 scale was used to evaluate adverse effects. Acute toxicity was defined as those complications that appeared between the end of treatment and for 3 months afterwards, while side effects observed from 3 months to the date of the last follow-up were considered as late toxicity. Patients were evaluated weekly during EBRT, then monthly until month 3 and at 3- to 6-month intervals thereafter.

## Results

Between February 2015 and July 2020, 26 men at a median age of 69.5 years (range 52–84 years) were referred with a diagnosis of prostate adenocarcinoma with a synchronous presence of lymph node or bone metastases and with an average and median PSA values of 32.5 ng/mL and 113 ng/mL (range 2.6–295) respectively. Three patients (12%) had Gleason ≤ 6, 8 (31%) Gleason 7, 7 (27%) Gleason 8 and 8 (31%) Gleason ≥ 9. Eighteen patients (69%) presented exclusively lymph node metastases, 4 (15.5%) bone metastases and 4 (15.5%) both lymph node and bone metastases simultaneously. Twenty-six per cent of the lymphatic metastases were located in the obturator nodes and 19% in the common iliac, external iliac and internal iliac nodes, respectively. The bone metastases settled mainly on the pelvic girdle, 30% in the sacroiliac region. Only in one case was bone metastasis observed in the spine outside the pelvis. Table 2 summarizes the complete characteristics of the series analyzed and Figure 1 shows the locations of metastases and their relative frequency.

Hormonal treatment with antiandrogens and gonadotropin releasing hormone (GnRH) analogues was prescribed as neoadjuvant therapy in 23 men (88%), with a median of 4 months (range 1–14) before radical intention radiotherapy of the primary tumor and oligometastatic localizations, and in 3 patients (12%) coinciding with the start of radiation therapy. In addition to ADT, 2 patients received 6 cycles of docetaxel and other 3 patients received abiraterone and prednisone at the time of diagnosis and continued with the treatment on last follow-up, having maintained systemic treatment for 12, 21 and 22 months, respectively.

**Table 2.** Patients' characteristics

| N = 26 | N (%) |
|---|---|
| Age: median (range) | 69.5 (52-84) |
| **PSA** | |
| Average | 32.5 ng/mL |
| Median (range) | 13 (2.6-295) ng/mL |
| **Grade group (Gleason score)** | |
| 1 (≤ 6) | 3 (12) |
| 2 (3 + 4) | 4 (15) |
| 3 (4 + 3) | 4 (15) |
| 4 (8) | 7 (27) |
| 5 (9–10) | 8 (31) |
| **T** | |
| 1c | 4 (15) |
| 2a | 1 (4) |
| 2b | 2 (8) |
| 2c | 4 (15) |
| 3a | 3 (12) |
| 3b | 8 (31) |
| 4 | 4 (15) |
| **N** | |
| 0 | 4 (15) |
| 1 | 22 (85) |
| **Metastases** | |
| Lymphnodes | 18 (70) |
| Bone | 4 (15) |
| Lymph and bone | 4 (15) |

PSA — prostate-specific androgen

With a median follow-up of 15.5 months (range 3–65 months), 16 patients (62%) are alive without evidence of local or distant relapse or progression while 10 (38%) are alive with local or distant tumor progression according to clinical and image performed exams. No patient has died during follow-up from cancer or of any other cause. Four patients (17%) have developed tumor progression in different locations during follow-up with a median time to progression of 43.5 months (range

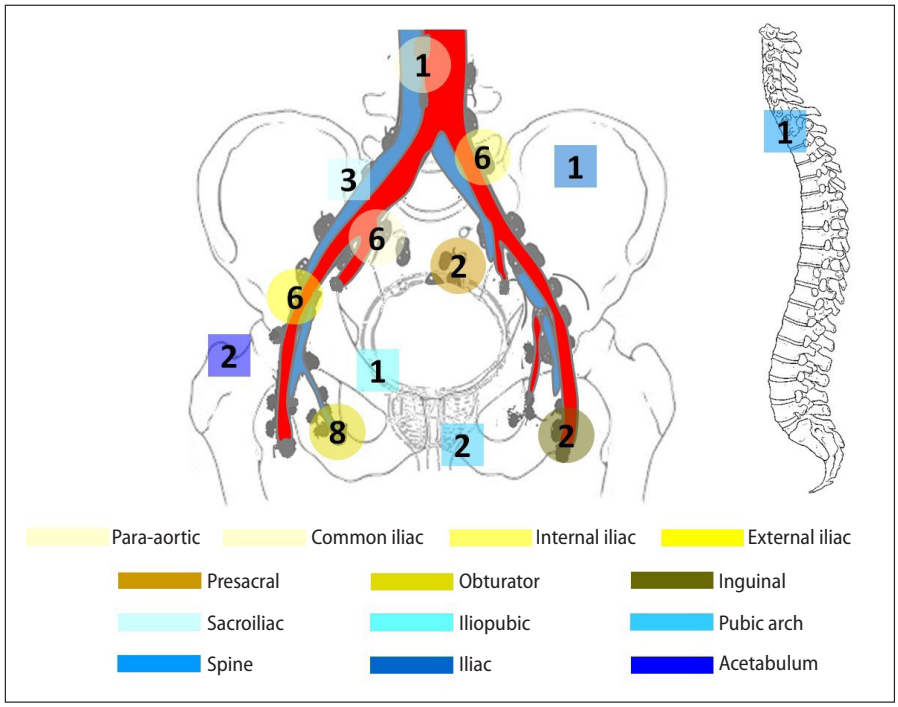


**Figure 1.** Number and location of de novo oligometastases in lymph nodes (circle) and bone (square)

27–56 months): lymph node metastases outside the pelvis in 2 patients, vertebral bone metastases in 2 patients, bone metastases in the iliac bone in one patient and pulmonary metastases in 1 patient. It should be noted that no recurrence during follow-up was observed in a previously irradiated area. In the 3 patients who presented lymph node and/or bone metastases, salvage radiotherapy was considered, administering doses of 25 Gy in 5 fractions on retroperitoneal lymph nodes with simultaneous boost up to 35 Gy in 5 fractions on macroscopically involved lymph nodes, a dose of 18 Gy in a single fraction on vertebral metastases and a dose of 35 Gy in 5 fractions in iliac bone metastases. Of these 4 patients with metastatic tumor progression, 2 restarted hormonal blockade with antiandrogen and LHRH analog while one patient received abiraterone and prednisone and, subsequently, cabazitaxel in the face of new lung progression, which they maintained until the date of the last follow-up. With a median time of 7 months (range 3–23) from the second irradiation, 2 patients are alive with progressing tumor and 2 patients are alive with no evidence of relapse or progression. We have not observed any case of resistance to castration, most likely due to the short follow-up period, which is why bRFS could not be adequately evaluated. The

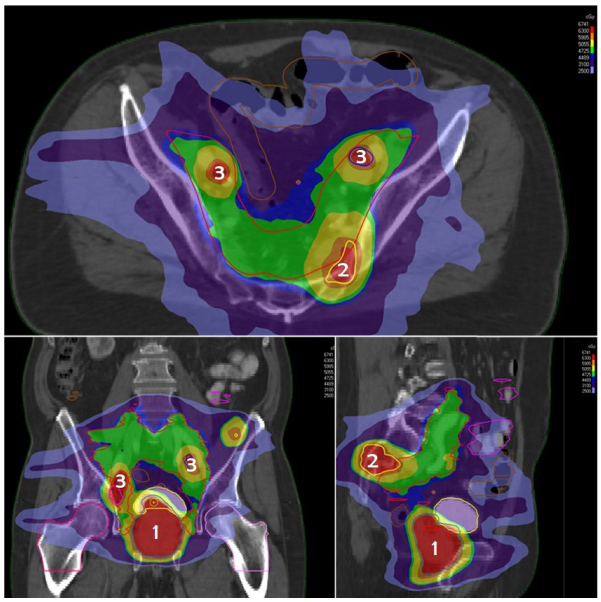


**Figure 2.** Dose distribution of simultaneous irradiation of prostate (1), bone metastases (2) and lymph node metastases (3)

actuarial PFS rates at 12 and 24 months were 94.1% and 84.7%, respectively (Fig. 2). Univariate analysis performed included age, PSA value at diagnoses, tumor stage, number and location of oligometastases, Gleason group grade classification and use of

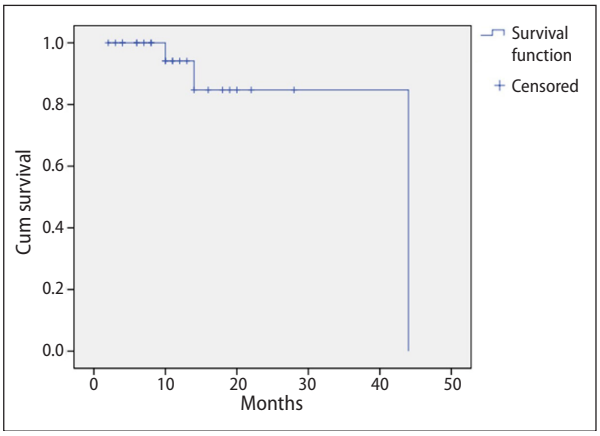


**Figure 3.** Kaplan-Meier curve for progression-free survival (PFS)

different systemic treatments. None of these factors studied in the univariate showed statistical significance.

Tolerance to treatment was acceptable. We did not observe cases of acute or late G3 or higher genitourinary or gastrointestinal toxicity. Fifteen patients (58%) presented acute genitourinary toxicity, 14 G1 and 1 G2, and 1 patient (4%) late G1 genitourinary toxicity. Seven patients (27%) had acute gastrointestinal toxicity of G1 in all cases and 1 patient (4%) had late G2 gastrointestinal complications (Tab. 3). Although the toxicity associated with hormonal treatment was not the objective of our study, we reviewed it without observing serious secondary complications, sexual dysfunction being the most relevant of them. Given the low relative number of patients on abiraterone, we are also unable to draw conclusions about related toxicity.

**Table 3.** Acute and late toxicities

| | Acute: N (%) | Late: N (%) |
|---|---|---|
| GIT | G1: 7 (26.9%)<br>≥ G2: 0 | G2: 1 (3.8%)<br>≥ G3: 0 |
| GUT | G1: 14 (53.8%)<br>G2: 1 (3.8%)<br>≥ G3: 0 | G1: 1 (3.8%)<br>≥ G2: 0 |

GIT — gastrointestinal toxicity; GUT — genitourinary toxicity; G — grade

## Discussion

Since Hellman and Weichselbaum defined the existence of an intermediate state between localized tumor and generalized metastatic disease, which they called an oligometastatic state, suggesting that these patients could have a more favorable behavior with better disease-free intervals and even longer survival, there has been a great interest in trying to identify more precisely these oligometastatic patients susceptible to more effective treatment [4]. The increasing use of more sensitive and precise diagnostic imaging tests, such as PET-choline, F18-fluciclovine PET or the most promising PET-PSMA, favors early identification of patients with oligometastatic prostate cancer at the time of first diagnosis (de novo oligometastatic prostate carcinoma) [7, 8].

The prognosis of de novo metastatic prostate adenocarcinoma seems to be directly related both to the tumor burden, referring to the number of metastatic sites, and to their anatomical location. The analysis by Gandaglia et al., performed on 3,587 men with de novo metastatic prostate cancer included in the SEER database, showed that the presence of visceral metastases represented a negative prognostic factor associated with significantly lower median overall and cause-specific survival than those patients with exclusively bone or lymph node metastases, the latter showing higher median survival rates [9]. Similarly, Halabi et al. published results of a meta-analysis including 9 phase III clinical studies with a total of 8,820 patients, observing that the presence of visceral liver or lung metastases is associated with a significantly worse survival compared to patients exclusively with lymph node and/or bone metastases [10].

The treatment of metastatic hormone-sensitive prostate cancer is a considerable challenge. In recent years, there has been a remarkable evolution, from the first studies that limited treatment to the administration of systemic hormonal treatment exclusively assuming that with a primitive tumor being widespread the importance of local treatment should be of less importance, until the most recent results of different randomized studies that have demonstrated the importance of prostate local treatment. The benefit of local treatment translates into improvements not only in biochemical relapse-free survival, but also in overall survival and cause-specific survival, especially in patients with low metastatic tumor burden. The HORRAD study that analyzed the impact of adding radiotherapy to hormonal treatment in patients with initial metastatic bone disease did not observe differences

between the 2 arms of the study, although the confidence interval (CI) cannot exclude a substantial survival benefit [11]. In the same way, the STAMPEDE study, although it did not find differences when radiotherapy to the primary tumor was added to systemic treatment, used the results in a prespecified subgroup analysis by metastatic burden and showed a significant benefit with radiotherapy with respect to failure-free survival, progression-free survival, cancer-specific survival and overall survival in patients with a low metastatic burden [12]. Further analysis by STAMPEDE also suggests that the benefit of radiotherapy would also extend to patients who present with de novo exclusive metastatic lymph node disease without the presence of bone or visceral metastases [13]. In the context of de novo disseminated tumor with a "low metastatic burden", local treatment is justified both in reducing the tumor burden, which can prevent the seeding of new metastases from both the primary and secondary lesions, as in the possible induction of systemic, abscopal effects, through immune activation induced by irradiation of tumor areas [14, 15]. Defining what is meant by "low metastatic burden" is a challenge yet to be tackled. Different studies have used different criteria to establish the low-risk group. The HORRAD study suggested a benefit, although not statistically significant, in patients considered "low-volume metastatic" characterized by the presence of less than 5 bone metastases, PSA < 142 ng/mL, and Gleason ≤ 8 [11]. Meanwhile, the STAMPEDE study applied the criteria defined by the CHAARTED trial to identify as "high metastatic burden" the existence of 4 or more bone metastases, at least one of them being outside the pelvis or spine, or the presence of visceral metastases to define the subgroup of patients benefiting from radiation therapy to the primary prostate tumor [12, 16]. A recent systematic review and meta-analysis of the HORRAD, STAMPEDE and the ongoing PEACE1 studies including a total of 2,126 men with de novo oligometastatic prostate cancer, demonstrated an increase in 3-year overall survival when adding radiation therapy to the prostate in patients with less than 5 bone metastases [17]. However, despite the observed survival gain, two aspects that appear relevant in the context of de novo oligometastatic prostate cancer patients should be highlighted. First, the doses of radiotherapy administered can be considered "low" in all 3 studies, lower than those currently recommended for the local treatment of prostate cancer. Assuming an alpha/beta value of 1.5 Gy for prostate cancer, the biologically effective dose ($BED_{1.5Gy}$) from the three studies would be as follows: 163.3–171 Gy (HORRAD), 155.8–180 Gy (STAMPEDE) and 172.7 Gy (PEACE1). It has long been known that moderate dose-escalation in prostate cancer radiation therapy above a $BED_{1.5Gy}$ of 180 Gy is associated with increased tumor control [19]. Our patients received a prescription of 63 Gy in 21 daily fractions, over 4.2 weeks, with a $BED_{1.5Gy}$ of 189 Gy both to the primary and metastatic lesions; a dose higher than those administered in the HORRAD, STAMPEDE, and PEACE1 trials. On the other hand, none of the 3 mentioned studies contemplated the option of treatment directed specifically to distant metastases. The systemic approach is considered the standard treatment for metastatic prostate cancer, with the addition of local treatment of the prostate in selected cases. Main goal of treating metastatic disease has traditionally been to alleviate the symptoms that metastases may cause. However, more recently, the concept of metastasis-directed treatment (MDT) has emerged with force for selected groups of patients. The STOMP (Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence) trial randomized 62 patients with oligorecurrent hormone-sensitive prostate cancer with up to 3 metastases to surveillance or metastasis-directed therapy (MDT) by surgery or SBRT. The 3-year results demonstrated the benefit of MDT in the primary endpoint of androgen deprivation therapy (ADT) free survival, maintaining the same quality of life in both groups of patients [19]. In 2020, the authors updated their 5-year data confirming 34% ADT-free survival in the MDT-randomized arm compared to 8% in the observation arm, and these results were independent of the location of metastases or of the speed of disease progression [20]. The ORIOLE (Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer) trial randomized 54 men with hormone-sensitive prostate cancer with 1–3 oligometastases to receive MDT with SBRT versus observation. With a median follow-up of 19 months, the primary goal of 6-month progression-free survival was 39% in the observation arm versus 81% in the MDT arm (p = 0.005) with no grade 3 or higher observed complications [21]. Fi-

nally, the PEACE V-STORM (Salvage Treatment of OligoRecurrent nodal prostate cancer Metastases) trial aims to analyze the impact of adding elective pelvic lymph node irradiation to the MDT of pelvic lymph node oligorrecurrences, planning to complete the study by the end of 2023 [22].

All patients included in our analysis received local treatment with radical intention on the primary tumor as well as metastasis-directed ablative radiotherapy on affected lymph nodes and bone metastases. Radiation therapy with ablative intent to both the primitive prostate tumor and the different metastatic sites could be an alternative with a curative intent to be evaluated in the context of the multidisciplinary approach to de novo oligometastatic prostate cancer. However, a limited number of studies have focused on developing this option. Table 4 summarizes the results observed by 5 groups that propose radiotherapy with a curative intent both of the primitive prostate tumor and of the metastatic sites in patients with de novo oligometastatic hormone-sensitive prostate cancer [23–27]. All included studies are retrospective and show some appreciable differences. First, there is no clear uniformity, beyond excluding the presence of visceral metastases, to identify the oligometastatic status for radical prostate treatment and MDT: Imber et al. include up to 6 metastases [26], Tsumura et al. up to 5 [24], Reverberi et al. less than 5 [25], while Deantoni et al. limit the inclusion to a maximum of 2 bone metastases [27] and Cho et al. do not specify this aspect [23]. Second, there are notable variations in irradiation schemes, fractionations, and total doses administered to both prostate tumors and oligometastases. To facilitate comparison, the $BED_{1.5Gy}$ of the different regimens has been calculated. The $BED_{1.5Gy}$ values administered to the prostate vary between 160–318 Gy while for MDT they vary between 70–156 Gy. Coincidence exists regarding the simultaneous use of ADT in all patients, although the use of other systemic treatments, such as abiraterone, enzalutamide or docetaxel shows great variations between the different studies. Finally, there is a coincidence in the acceptable tolerance of the treatments, with rare occurrence of acute and late genitourinary or gastrointestinal toxicity equal to or greater than grade 3. Our results compare well with those reported by other groups, although the duration of follow-up is somewhat shorter.

We are aware of some strengths and weaknesses of our study. All patients received identical hypofractionated radiation treatment, with doses that can be considered high both on the prostate and on MDT and similar to those used for curative radical radiotherapy in patients with localized non-metastatic prostate cancer. We are also aware that one of the main criticisms of our work is that, strictly speaking, the consideration of the presence of pelvic lymph node metastases as oligometastasis can be discussed. However, it is a common practice in other studies on the treatment of oligometastatic prostate cancer [20, 21, 24, 25]. Also, all included patients were on ADT, which could contribute to making an exact and consistent evaluation of treatment response difficult. Likewise, the low number of patients, the short follow-up and the retrospective nature of this study oblige us to be cautious with these results and to wait for longer follow-up.

## Conclusion

The increasing precision and accuracy of imaging tools is leading to an increase in the de novo diagnosis of prostate carcinoma with the simultaneous presence of a low number of metastases (oligometastasis), and represents a challenge for those involved in the treatment of these patients. The possibility of performing radical radiation therapy with moderate hypofractionation for curative intent of both primary prostate tumor and metastatic sites is a real option for selected patients with good rates of tumor control with acceptable tolerance. However, more randomized studies with greater recruitment and follow-up are still required to confirm these good results.

### Conflict of interests

The authors declare that they have no competing interests.

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We declare no source of funding for any aspect of research reported.

### Authors' contribution

A.M., D.G. and V.C. collected, analyzed and interpreted the patient data and wrote the whole manuscript; O.H., X.C., J.V. and C.R. were major contributors in writing the manuscript; P.G.A., A.P.

**Table 4.** Studies of prostate and metastases-directed radiation therapy in oligometastatic prostate carcinoma

| Author | Oligometastases criteria | N | Study type | Follow--up | Prostate: total dose/fractionation | Metastases dose/ /fractionation | $BED_{1.5Gy}$ prostate | $BED_{1.5Gy}$ metastases | Systemic treatment | Toxicity | Results |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cho 2016 | NE | 38 | Retro-spective | 34 | Median dose: 60 Gy/2.5 Gy × 20 | Median dose: 40 Gy/4 Gy × 10 | 160 | 146.7 | ADT 100% | No ≥ G3 GU/GI | OS (3 y): 69%<br>bRFS (3 y): 52% |
| Tsumura 2019 | ≤ 5 non–visceral metastases | 40 (MDT = 18 *vs.* No-MDT = 22) | Retro-spective | 62.5 | BT+EBRT: 37.5 Gy/7.5 Gy × 5 + 30–40 Gy/2–3 Gy × 20–10 | 30–50 Gy/ /2 Gy × 15–25 | 315–318.3 | 70–116.7 | ADT 100% | Acute GI/GU ≥ G2: 5.5%/16.6%<br>Late GI/GU ≥ G2: 0%/5.5% | CRFS:<br>MDT > No–MDT (HR 0.319, 95%CI: 0.116–0.877) |
| Reverberi 2020 | < 5 non-visceral metastases | 37 | Retro-spective | 55.5 | 68.75 Gy/2.75 Gy × 25 | 45–60 Gy/ /1.8–2.4 Gy × 25 | 194.8 | 99–156 | ADT 97.3%<br>Docetaxel 2.7% | Acute GI/GU G2: 20%/20%<br>Late GI/GU G1: 2.7%/18.9% | OS (5 y): 65.4%.<br>bRFS (5 y): 39.3%.<br>LRFS (5 y): 83.7%. |
| Imber 2020 | 1 to 6 metastases | 47 | Retro-spective | 27 | Various schedules:<br>Conventional fractionation: 81 Gy/1.8 Gy × 45<br>Moderate hypofractionation: 70.2 Gy/2.7 Gy × 26<br>55–70. 2 Gy to<br>SBRT: 40 Gy/8 Gy × 5<br>EBRT+BT: 45 Gy/1.8 Gy + 15 Gy HDR or 45 Gy/1.8 Gy + 100 Gy LDR | Various schedules<br>Median dose: 27 Gy/9 Gy × 3 | 178–253.3 | 189 | ADT 100%<br>Abiraterone 25.7%<br>Enzalutamide 2.1%<br>Docetaxel 4.3% | NR | OS (2 y): 87%<br>bRFS (2 y): 77%<br>FFDM (2 y): 78% |
| Deantoni 2020 | ≤ 2 bone metastases | 39 | Retro-spective | 42.6 | Median dose: 74.2 Gy/2.65 Gy × 28 | Median dose: 44 Gy/2 Gy × 22 | 205.3 | 102.7 | ADT 100% | No > G2 acute GU/GI<br>Late GU G3: 2.6%; G4: 2.6% | OS (4 y): 82.4%<br>bRFS (4 y). 53.3%<br>CRFS (4 y): 65.7%<br>FFDM (4 y): 73.4% |
| Current series | Non–viisceral metastases | 26 | Retro-spective | 15.5 | 63 Gy/3 Gy | 63 Gy/3 Gy | 189 | 189 | ADT 100% | Acute GI/GU ≥ G2: 0/4%<br>Late GI/GU ≥ G2 4%/0 | PFS (1 y): 94.1%<br>PFS (2 y): 84.7% |

ADT — androgen deprivation therapy; BED — biological effective dose; EBRT — external beam radiation therapy; BT — brachytherapy; HDR — high-dose rate; LDR — low-dose rate; GU — genitourinary; GI — gastrointestinal; OS — overall survival; bRFS — biochemical relapse free survival; MDT — metastases directed therapy; LRFS — local relapse free survival; CRFS — castrate resitence free survival; FFDM — freedom for distant metastases; PFS — progression free survival; NR — not reported

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