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Radiotherapy of Oligometastatic Prostate Cancer: Experience of the Mohamed VI Center for Cancer Treatment in Casablanca, Morocco

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Abstract :-

➢ ***Backgraound***

Oligometastatic disease is an intermediate stage between locally advanced disease and multi-metastatic disease. We report the experience of the Mohamed VI Center for the Treatment of Cancers in the management of oligometastatic prostate cancers in a retrospective series from 2016 to 2019.

➢ ***Method***

We collected cases of de novo metastatic prostate adenocarcinoma judged to be oligometastatic and having benefited from radiotherapy on the prostate. The primary endpoints were: progression-free survival and overall survival at 2 and 3 years. The proportions were compared by the CHI 2 test with a significance level of 0.05. The Kaplan Meier model was used to compare survivals.

➢ ***Result***

We had recruited 37 patients with a median age of 70 years. The initial PSA was between 11 ng/ml and 1635 ng/ml with an average of 160 ng/ml. The Gleason score was between 8 and 10 in 46 % of patients. A secondary bone location was present in 100% of cases and no patient had a visceral metastasis. The vertebral seat was the most common secondary bone site (55%). The maximum number of metastatic sites was 3. The median follow-up is 38 months. Overall survival at 24 months and 36 months, respectively, was 92% and 86%. The 2-year and 3-year progression-free survival was 84% and 79%, respectively. There was no statistically significant difference in either overall survival or progression-free survival between patients who received radiation to the prostate alone and those who received radiation to the prostate plus the pelvis (p = 0.86). No significant difference was observed in terms of survival between the patients who received in addition to local radiotherapy and primary palliative chemotherapy and those who received only local radiotherapy. The low statistical power of our sample did not allow us to obtain a significant difference between patients irradiated in hypofractionated and those irradiated in conventional fractionation.

➢ ***Conclusion***

The limit of our study lies in the small size of our sample but also in its retrospective nature. Prostate radiation therapy remains a treatment option for de novo oligometastatic prostate cancer.

Keywords:- *Prostate, Adenocarcinoma, Metastasis, Radiotherapy, Morocco.*

I. INTRODUCTION

Hellman and Weichselbaum pioneered the concept of oligometastatic disease in 1995 [1]. It is an intermediate stage between locally advanced disease and multi-metastatic disease [2]. This concept of oligometastasis has largely evolved with imaging techniques and therapeutic possibilities. In practice, the qualification of oligometastasis uses various notions such as the metastatic mass, the number of metastases detectable in imaging, the number of organs affected, the number of subunits within an organ which can be decisive in terms of therapeutic possibilities [3]. However, the definition of oligometastatic prostate cancer varies in the literature [4]. It depends on the number of metastases, the type of imaging, and the site of the metastases. Most publications set the maximum number of metastases at 5. Conversely, in other clinical trials, a lower number of secondary locations (< 3) was necessary to define oligometastatic cancer [5]. Our study aims to report the experience of the Mohamed VI Center for the Treatment of Cancers in the management of oligometastatic prostate cancers.

II. METHOD

We retrospectively collected all patients with de novo metastatic prostate cancer judged to be oligometastatic on the basis of CT and scintigraphy and who received radiotherapy to the prostate in the period from 2016 to 2019. Patient monitoring was quarterly by the PSA. Biological progression was defined by the rise of the PSA to more than

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2 ng/dl plus the nadir PSA. We used as a data collection source the computerized patient registration system of the Mohamed VI center for the treatment of cancers in Casablanca. Data entry and analysis were performed using SPSS software version 21. The proportions were compared using the CHI 2 test. The ORs adjusted by a logistic regression model were also presented with their 95% CIs with a significance level of 0.05. We used the Kaplan Meier model to compare survival from the time of diagnosis.

III. RESULTS

We recruited 37 patients with a minimum age of 57 years and a maximum age of 88 years with a median age of 70 years. The majority of patients were brown-skinned, 76%. Thirty of the 37 patients had no comorbidities. A family history of prostate cancer was found in 3 patients. The majority of patients had a good general condition at the first consultation, i.e. 19%, 78% and 3% respectively for a WHO performans status (PS) of 0; 1 and 2. The initial PSA was greater than 20 ng/ml in 84% of cases. None of the patients had a PSA lower than 10 ng/ml. The extreme values of the initial PSA were 11 ng/ml and 1635 ng/ml with an average of 160 ng/ml. There was already bone symptoms in 16% of cases at the time of diagnosis. In terms of extension assessment, all the patients had performed the thoraco-abdomino-pelvic CT, only one patient had not performed the scintigraphy at the time of diagnosis. Choline PET was performed in only 16% of patients and those following progression or relapse. Prostatic adenocarcinoma was the only histological type found. Prostate biopsy was the most common mode of diagnosis at 84%. We noted 46% of Gleason score between 8 and 10; 43% had a Gleason score of 7 and only 11% (04 patients) had a Gleason score of 6. For the poor prognostic factors, we found the presence of vascular embolism and perineural ensheathing respectively in 38% and 49% of cases. No patient had visceral metastasis. A secondary bone localization was present in 100% of cases. A lumbo-aortic lymph node localization was found in 3 patients in addition to the secondary bone localization. The vertebral location was the most frequently encountered secondary bone site. The maximum number of secondary sites in a patient was 3. There were no more than 2 vertebral levels affected in the same patient. On the whole of the vertebral column there were no more than 3 vertebrae affected. Half of the patients had only 2 bone secondary localization sites. For treatment, we found that 13 of the 37 patients received docetaxel-type chemotherapy in addition to hormone therapy. This chemotherapy was instituted before radiotherapy, it concerned patients who had pain but also those who had a high PSA level. Chemotherapy was done with docetaxel on 21 days. Among the 13 patients who had chemotherapy, 3 needed a second line before radiotherapy, including 2 patients with carboplatin and 1 with etoposide + cisplatin. The total number of cures was 9 in 1 patient, 8 in 1 patient also, 7 in 04 patients and 6 in 07 patients. Only one patient benefited from a laminectomy. All 37 patients underwent radiotherapy of the prostate, 28 of which were intensity modulated (Table1). Analgesic radiotherapy on the bone metastasis was performed in 4 patients before local radiotherapy on the prostate. The majority of patients (76%) were irradiated at the same time on the prostate and the pelvic lymph nodes in prophylaxis, with 74 Gray in conventional fractionation. In addition to local radiotherapy, all patients received hormone therapy, with LHRH analog in 20 patients and by pulpectomy in 17 patients. Side effects of treatment were observed in 65% of patients. The complications found are, among others, acute radiodermatitis grade 2, radiation proctitis, hot flushes, gynecomastia, sexual weakness respectively in 11% of cases, 11%, 24.3%, 14%, 49% of cases (Table 3).

Table 1 Description of Radiotherapy

	n	***%***
TYPE OF RADIOTHERAPY		
VMAT	28	75.7
3D	9	24.3
RADIOTHERAPY SITES		
Primitive alone	33	89.2
Primitive + metastasis	4	10.8
IRRADIATION VOLUME		
Prostate + lymph nodes	28	75.7
Prostate alone	9	24.3
DOSE AND FRACTIONATION		
60 Gray in 20 fractions	9	24.3
74 Gray 37 fractions	28	75.7

Table 2 Patients Characteristics

	n (%)
GLEASON SCORE	
Gleason 6	04 (11%)
Gleason 7	16 (43%)
Gleason 8	09 (24%)
Gleason 9	07 (19%)
Gleason 10	01 (03%)

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BONE SITES OF METASTASIS	
Vertebrate	28 (55%)
Pelvic	19 (37%)
Femur	01 (02%)
Scapula	03 (06%)
DISTRIBUTION OF VERTEBRAL METASTASIS	
Cervical	01 (03%)
Thoracic	16 (50%)
Lumbar	11 (34%)
sacred	04 (13%)
NUMBER OF METASTASIS	
1	15 (42%)
2	18 (50%)
3	03 (08%)

For the response to treatment, 81% remission was noted 3 months after the end of radiotherapy with a total PSA of less than 2 ng/ml. Among the 07 patients who were in progression, 02 were in biological progression and 05 in biological and radiological progression. Deaths at 3 years of follow-up were 08, including 02 patients who died of coronavirus infection (COVID 19) with PSA levels remaining undetectable. Overall survival at 24 months and 36 months, respectively, was 92% and 86%. The median follow-up is 38 months with extremes of 10 months and 60 months. Patients alive and in biological and radiological progression are 22%. In univariate analysis, there is no statistically significant difference in overall survival or progression-free survival between patients who received irradiation of the prostate alone and those who received irradiation of the prostate plus the pelvis. The same was true between those who received radiotherapy of the primary alone and those who received radiotherapy of the primary plus the bone metastasis. No significant difference was observed in terms of survival between the patients who received in addition to local radiotherapy and primary palliative chemotherapy and those who received only local radiotherapy (figure 1).

Table 3 Treatment Complications

	n	***%***
Grade 2 radiodermatitis	04	10.8
Grade 4 aplasia	01	02.7
Radiation cystitis	01	02.7
Radiation proctitis	04	10.8
Gynecomastia	05	13.5
Hot flush	09	24.3
sexual weakness	18	48.6
Urinary incontinence	01	02.7

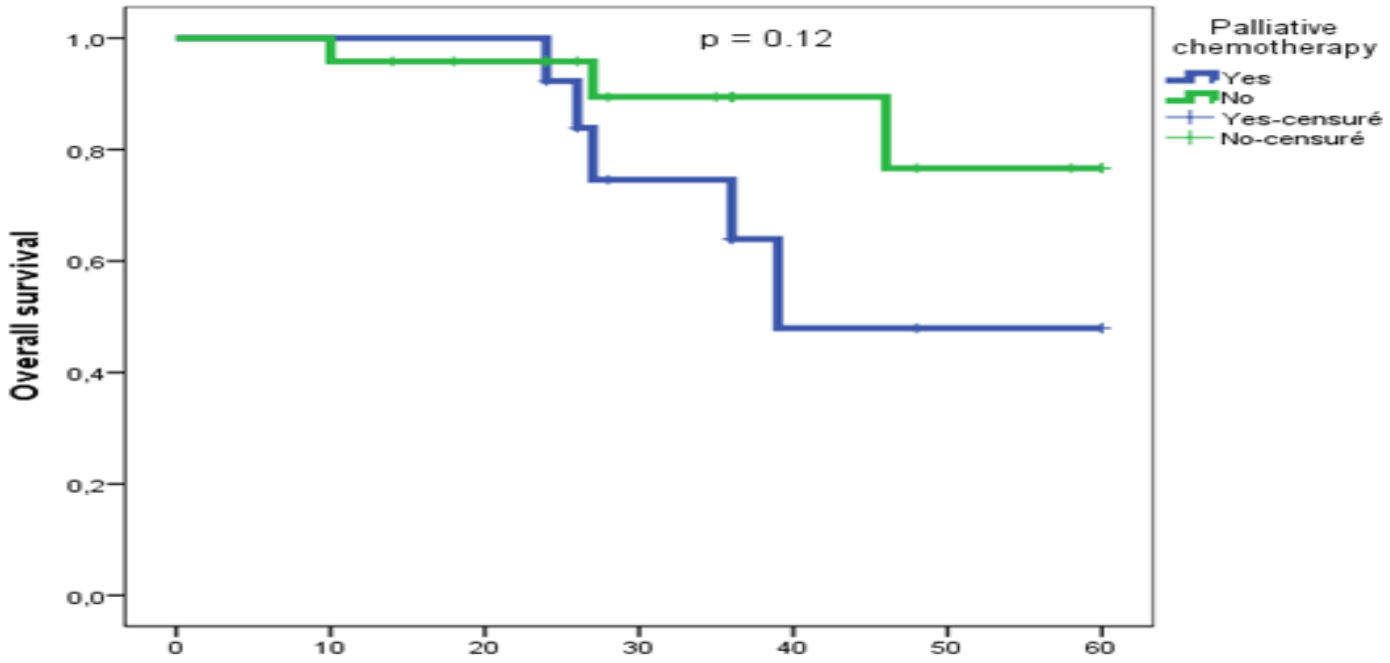

Fig 1 Overall Survival Curve According to Chemotherapy

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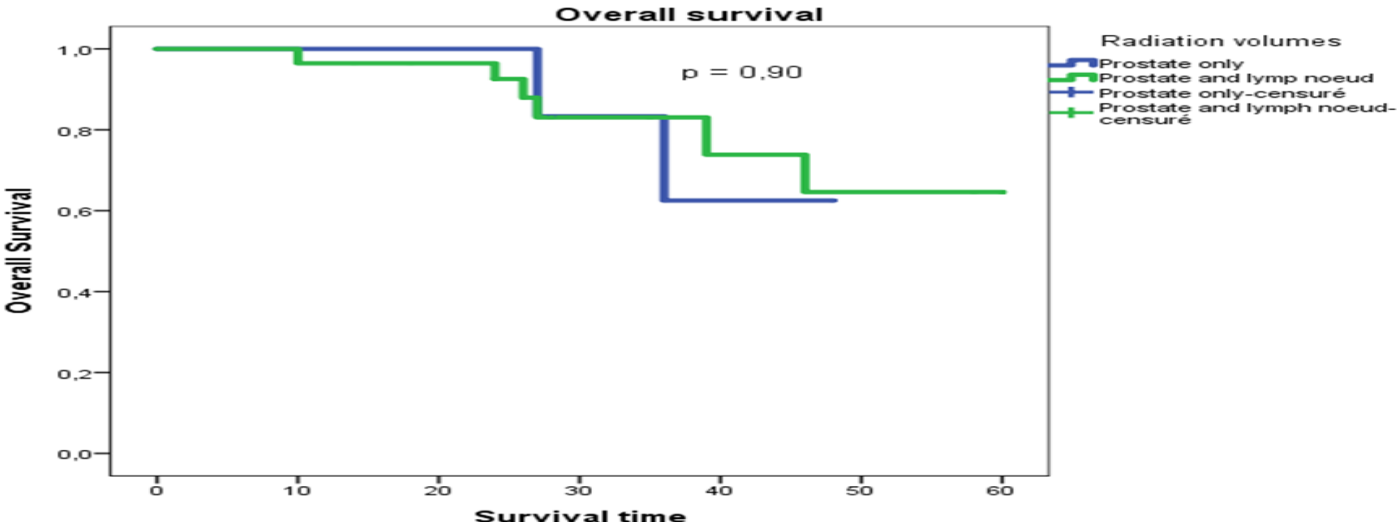

Fig 2 Curve of Overall Survival According to the Volume of Irradiation

IV. DISCUSSION

The definition of oligometastatic disease remains heterogeneous to this day. In the literature, the number of 5 maximum bone metastases is the number of secondary locations accepted to remain in the oligometastatic [6, 7, 8]. In our study, the maximum number of metastatic sites was 3. However, it is recognized that the diagnosis of the oligometastasis stage depends on the capacity of the imaging used for the extension assessment [9]. Currently, the standard metastatic assessment recommended by learned societies for prostate cancer is scintigraphy and computed tomography [10]. However, with advances in molecular imaging techniques, more and more metastases are being detected. This do that, many patients considered as non-metastatic in conventional imaging could have an oligometastatic disease, just as an oligometastatic disease could turn out to be polymetastatic with the new imaging techniques (PET-choline and PET-PSMA). Positron emission tomography using choline (PET-choline) has a relatively good specificity of 89.5 to 99.7% and a positive prediction unlike bone scintigraphy which has a specificity and sensitivity around 65%, which implies that part of the metastases is not detected in the standard assessment [8, 11].

The most promising radiotracer in metabolic imaging is PSMA (Prostate Specific Membrane Antigen) mainly due to increased avidity of the absorption at PSA thresholds below 5 ng/dl [11]. In 15 patients with localized prostate cancer considered high risk on scintigraphy and CT, Sterzing et al. using PSMA PET in a staging, noted that 09 of the 15 patients in the study had synchronous metastatic lesions [12]. In our cohort PET with choline was performed in only 16% of patients and those following progression or relapse. Bone is the most frequent site of metastatic invasion, and often even the only one in prostate cancer [13]. They represent 70% of metastases and occur mainly in the axial skeleton [14]. These bone metastases, which may initially be asymptomatic, unfortunately frequently evolve into multiple complications such as pain, fractures, spinal cord or radicular compression, symptomatic hypercalcemia or spinal cord insufficiency. The number of bone metastases and their axial or peripheral location represent a major prognostic factor [13]. In our cohort, 38% of patients had a single bone metastasis and the vertebral location was the most represented at 55%. No visceral metastasis was found. We did not note any significant difference in terms of survival according to the number of secondary locations due to the low statistical power of our sample. For a long time, metastatic cancers from the outset were unequivocally considered to have an unfavorable prognosis and only systemic treatments were considered [15]. Oligometastatic disease appeared to be a clinical and prognostic entity in which the place of local treatment (of the primary lesion and/or metastases) would make it possible to lengthen overall survival or to delay the progression of the disease [6]. At the biological level, the local irradiation of the primitive in addition to preventing the formation of cytokines and circulating tumor cells, would interrupt the process of self-censorship and the formation of metastatic niches. Radiotherapy would also make it possible to eliminate pro-genitor cells at the origin of resistance to systemic treatments [16]. Lymphocyte activation via pro-inflammatory molecules resulting from radiation-induced cell death could induce an anti-tumor immune response [17,18]. This immunomodulatory action of radiotherapy associated with the abscopal effect described since 1953 constitutes a source of enthusiasm in the treatment of cancer to improve overall survival or to delay the progression of the disease. As regards oligometastatic prostate cancer, prostatic irradiation could limit the capacity of the primary tumor to potentiate the metastatic process [6]. To date, there is no international consensus on the local treatment of metastatic prostate cancer. In patients with locally advanced or metastatic prostate cancer, the meta-analysis by Cameron et al. analyzed nine retrospective studies dealing with symptomatic palliative pelvic irradiation. The symptom response rate was 75% (73% for haematuria, 80% for pain, 63% for bladder obstruction, 78% for rectal symptoms, 62% for ureteral obstruction). This publication did not allow a useful conclusion on total dose, fractionation pattern, dose–response effect or duration of response. The toxicity report was not systematic and only one study used a validated scale [19]. In our cohort, only one patient was not completely

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relieved of his symptoms and retained the urinary incontinence he had at the time of diagnosis. Prostatic radiotherapy is therefore an effective symptomatic treatment even in a metastatic situation. In the literature, we find retrospective and prospective studies that testify to the interest of irradiating the prostate in situations of oligometastasis, but without significant statistical value for these studies. There are 08 retrospective series suggesting the contribution of the treatment of the primary tumor in improving the overall survival of prostate cancer at the metastatic stage. These series are taken from the SEER (Surveillance, Epidemiology and End Results database) and the NCDB (National Cancer Data Base) [20 - 26] with an Asian series [27].

Culp et al. studied 8185 metastatic patients in the SEER database. The probability of overall survival at 5 years was significantly improved in patients treated locally with brachytherapy or radical prostatectomy compared to those who received no treatment (67.4% and 52.6% versus 22.5%). Local treatment was associated with a reduction in the relative risk of specific mortality in multifactorial analysis (32% for brachytherapy (HR: 0.38, 95% CI: 0.27–0.53, p < 0.001) and 62% for surgery (HR: 0.62, 95% CI: 0.49–0.93, p = 0.018)) [20]. Löppenberg et al. identified 15,501 patients with metastatic cancers from NCDB, including 1,470 treated locally (77% of them by irradiation). Compared to patients who did not receive local treatment, the probability of overall survival at 3 years was higher (69 versus 54%, p < 0.001). Age and the absence of local treatment were found to be predictors of mortality in multifactorial analysis [21]. In our cohort, all patients received radiotherapy to the prostate. Overall survival at 03 years was 86% (02 deaths are caused by COVID 19 infection) with relapse-free survival at 81%. Two prospective studies and a meta-analysis also demonstrated the benefit of prostate radiotherapy in prostate cancer in the oligometastatic subgroup. The phase III HORRAD trial [28] compared androgen suppression alone with androgen suppression associated with prostate irradiation. No difference was observed in this trial in overall survival or in survival without biological failure. Better overall survival was found only in patients with less than 5 bone metastases (HR: 0.68; 95% CI: 0.42–1.10, p = 0.063). The criticism made of the HORRAD trial is that it contained 60% of patients with high metastatic volume. The prospective phase III STAMPEDE trial [29] recently compared 2062 patients assigned to androgen suppression alone versus androgen suppression plus radiotherapy. There were respectively 40% and 54% of patients with low and high metastatic load according to the CHARTED criteria [30]. The STAMPEDE results showed no significant improvement in overall survival over the entire cohort (HR: 0.92; 95% CI: 0.8–1.06; p = 0.27) on the other hand, failure-free survival a was significantly prolonged in the radiotherapy arm (HR: 0.76, 95% CI; 0.68–0.84; p < 0.0001). Patients with a low number of metastases had significantly longer overall survival as well as failure-free survival (HR: 0.68; 95% CI: 0.52–0.90; p=0.007). The ST0P-CAP meta-analysis [31] which combined the two randomized trials (HORRAD and STAMPEDE) confirmed the interaction between the number of metastases and overall survival (HR; 1.47, 95% CI 1, 11–1.94, p=0.007). The overall survival probability was improved by 7% at 3 years of follow-up in patients with oligometastatic cancer. The ST0P-CAP meta-analysis [31] which combined the two randomized trials (HORRAD and STAMPEDE) confirmed the interaction between the number of metastases and overall survival (HR; 1.47, 95% CI 1, 11–1.94, p=0.007). The overall survival probability was improved by 7% at 3 years of follow-up in patients with oligometastatic cancer. The ST0P-CAP meta-analysis [31] which combined the two randomized trials (HORRAD and STAMPEDE) confirmed the interaction between the number of metastases and overall survival (HR; 1.47, 95% CI 1, 11–1.94, p=0.007). The overall survival probability was improved by 7% at 3 years of follow-up in patients with oligometastatic cancer. To date, we can therefore say that radiotherapy of the prostate has its place in the management of oligometastatic prostate cancer (less than 5 bone metastases or low volume according to CHAARTED). What remains to be demonstrated by clinical trials is the fractionation and the volumes to be irradiated. Although in the STAMPEDE trial the hypofractionated regimen on the prostate alone showed longer failure-free survival (HR: 0.69, 95% CI: 0.59–0.80, p < 0.0001) compared to the weekly schedule, it is necessary to have a "be to be" comparison in a randomized trial. The low statistical power of our sample did not allow us to obtain a significant difference between patients irradiated in hypofractionated and those irradiated in conventional fractionation.

Taking into account the low alpha/beta ratio of prostate cancer [32], a hypofractionated regimen could be adapted to the metastatic form in order to reduce the duration of treatment [8]. There are many trials which are in progress and which will make it possible to further clarify the place of local radiotherapy in metastatic prostate cancer. We have among others the French phase III multicenter trial PEACE 1 which is in the process of analysis, randomized in 4 arms which compares the combination of androgen suppression with chemotherapy by docetaxel with or without prostatic irradiation (of 74 Gy in 37 fractions) with or without abiraterone acetate and prednisone [33]. The phase III study NCT03678025 from the South-west Oncology Group (SWOG) compares the association of surgery or irradiation of the prostate with systemic treatment [34]. The phase II randomized Canadian trial PLATON, which is in the process of being recruited, will compare standard treatment with or without ablative treatment (radiotherapy or surgery) for all the locations of the disease [35]. A Croatian phase II study (NCT02913859) aims to determine the impact of radiotherapy in combination with androgen suppression on progression-free survival [36]. The IP2-ATLANTA trial is a phase II trial that compares minimally invasive surgery (cryotherapy or high-intensity focused ultrasound treatment) in 3 arms to standard treatment as well as radiotherapy treatment (60 Gy in 20 fractions or 74 Gy) or radical prostatectomy [37]. For people with early oligometastatic prostate cancer, with longer life expectancy and minimal comorbidities, for whom treatment remains a prudent consideration, further research is needed to identify appropriate treatment paradigms. For example, it

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remains unclear whether ablative therapy at the primary site alone, at primary and regional sites of disease, or at the primary site and all remote sites involved is required in the de novo oligometastatic setting. The limit of our study lies in the small size of our sample but also in its retrospective nature.

V. CONCLUSION

Today, in the absence of data and recommendations, the treatment of oligometastatic disease can be considered as a quality-of-life-oriented approach, with a personalized strategy for each patient depending on the balance. The prognosis of oligometastatic cancers being favorable compared to the metastatic cancers, prostate radiotherapy should be a standard treatment option for newly diagnosed patients with a low metastatic burden.

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