

Research Article

Treatment of Oligometastatic Prostate Cancer with Stereotactic Body Radiation Therapy

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Abstract

Introduction: 5% of new cases diagnosed with prostate cancer (PCa) are metastatic from its beginning. Of all the cases treated with curative intention, about 10-15% will progress to metastatic disease. There is a growing interest in being more aggressive in the approach these tumors in order to improve their survival.

Objectives: Stereotactic body radiation therapy (SBRT) is a commonly technique used in the treatment of oligometastatic (om) disease in other type of tumors. We present our short and medium term oncological results and toxicity using this technique or the treatment of omPca

Methods: Between October 2010 and July 2017 an amount of 34 patients with 80 metastasis (69 nodal and 11 bone metastasis) were treated at our institution with doses between 81 and 115 Gy. We included 21 patients with concomitant Androgen deprivation therapy (ADT) and 13 without. None of them were castration resistant.

Results: Mean age was 62 years and mean follow up of 72 months from primary treatment and 18 months from SBRT. 24 patients had exclusive nodal disease, 7 only bone disease and 3 bone and nodal disease. 27 patients presented complete response and 2 stable disease at the moment of the final analysis. 5 patients presented recurrent metastasis. 5 of them referred mild toxicity, 3 of them gastrointestinal and 1 urinary.

Conclusions: SBRT is a safe technique, with mild toxicity that allows an optimum biochemical and radiologic control at medium term, and it is able to delay systemic therapies.

INTRODUCTION

According to Spanish prostate cancer registry, 4% of newly diagnosed prostate cancers (PCa) are metastatic at the time of diagnosis [1]. Between 27 and 53% of PCa treated with curative intent will present a biochemical recurrence. Whilst a rising PSA level universally precedes metastatic progression [2].

In recent years we have seen an increase in interest in prolonging survival in patients with advanced stages of the disease. New drugs have been developed that prolong survival in stages of resistance to castration before and after the appearance of metastases and in patients with metastatic debut.

Patients diagnosed with a limited number of PCa metastases have a better prognosis than patients with a high metastatic volume or visceral metastases [3,4].

Low metastatic volume, limited typically in 5 or less distant metastatic regions, can be divided in 4 scenarios [5]:

- 1) Oligometastases: Noted at the time of diagnosis and the primary tumor was not treated.
- 2) Oligorecurrence: Patients treated with a curative

intention and whom during their follow-up presented recurrence outside the primary location

- 3) Oligoprogression: Relapse in one or more metastases (not exceeding 5) when the patient had received systemic treatment for the metastatic disease.
- 4) Induced oligometastases: When the systemic treatment of metastatic diseases left some untreated.

The aim of the study was to present our experience with SBRT for oligometastatic and oligorecurrence PCa proving local control with minimal toxicity.

MATERIAL AND METHODS

We analyzed a retrospective cohort of 34 patients diagnosed with oligometastatic PCa (5 or less metastatic lesions) treated by SBRT from October 2010 to July 2017. The patients had a total of 80 lesions. Treatment plans were designed using Pinnacle (Philips) software with daily image orientation using TrueBeam linac. Treatment sites included bone (n = 11) and lymph nodes (n = 69). In each case, the number of fractions and the prescribed doses per session were individualized based on the location and number of metastases. For bony metastases, 9 Gy in

3 fractions were administrated and for nodal metastases, 7,5 Gy in 6 fractions (equivalent dose of 81 Gy and 115 Gy respectively calculated on the bases of $\alpha/\beta = 1,5$ Gy). Response to treatment was assessed with PSA levels and imaging techniques (RECIST / PERCIST criteria). Toxicity was registered according to RTOG/ EORTC criteria. We included patients treated with and without ADT in the study. We excluded castration-resistant PCa. Statistical analysis was performed using SPSS v.20 (IBM).

RESULTS

Mean patient age was 62 years. Median follow-up was 72 months (range 39-228 months) since the first treatment and the median follow-up since SBRT treatment was 18 months (range 1,6-74 months). Mean PSA at initial diagnosis was 10,91 ng/ml (range 4,63-76,3 ng/ml). Primary therapies and Gleason score are listed in Table 1.

Mean PSA was 0,1 ng/ml (range 0-28,3 ng/ml) after treatment with curative intent, and 4,69 (range (2,3-18,3 ng/ml) at the time of biochemical recurrence, with a median PSA doubling time until biochemical recurrence of 4,23 months (range 0,19-12,2 ng/dl). The median biochemical progression-free from initial treatment was 41,5 months (range 4-84). Most of the patients received neoadjuvant ADT as listed in Table 2.

Metastatic evaluation was performed with [11C] Choline PET/TC in 32 patients whereas TC and bone scan was performed in 2 patients. Regarding the locations of the oligometastases, 24 patients presented with exclusively lymph node disease, 7 patients with exclusively bone disease and 3 patients with both. Resulting in 11 bone lesions and 69 lymph nodes treated. 5 patients had radiological relapse after SBRT treatment of which 4 had exclusively lymph node disease and 1 had bone disease. Only one patient recurred after the second treatment at the end of follow-up with an exclusive lymph node relapse.

Complete Biochemical response was observed in 27 patients (defined as a PSA reduction > 50%) whereas stable disease was observed in 2 patients (defined as PSA increase or decrease less than 10%) at the end of the follow-up. The median progression-free survival was 16,8 months (range 1,6-46 months)

PSA reduction > 50% was observed in 25 patients (73,5%) and PSA reduction > 25% in 29 patients (85,3%) after first SBRT treatment. Of the 4 patients who relapsed during follow-up, none had PSA reduction > 50. These 4 patients underwent a second SBRT treatment and had a median PSA of 4,8 ng/mL (range 0,8-11) at the time of second treatment.

Considering only the 13 patients who did not receive TDA, 9 patients presented a PSA response > 50%, 2 patients PSA response >25%, 1 patient a stable disease and 1 patient presented a progressive disease. In 30 patients (88,2%) no acute or late toxicity was observed. 3 patients presented urinary grade 1 toxicity and 1 patient presented rectal grade 1 toxicity. Throughout the follow-up, 1 of the patients died due to disease progression. Summary of our results is shown in Table 3.

DISCUSSION

Since the 19th century, we have assisted in the generation of different theories to explain the dissemination of PCa. In 1884, Halsteddescribed the dissemination by contiguity proposing that bone metastasis always precedes lymph node metastasis [6]. In 1980, Keynes and Fisher proposed the systemic theory, which states that prostate cancer is metastatic from the beginning by microscopic disease [7,8]. It was not until 1995 when Hellman and Weichselbaum presented their theory. This theory explains that in subclinical phase, the tumor has very low disseminative capacity, and in clinical phase it begins to acquire it [9]. Therefore, most of the time it stays in localized disease o preclinical phase and it is only over time, that the tumor acquires invasive and metastatic capacity.

Although the acquisition of this metastatic capacity is important, this theory does not explain 100% of metastases. It requires a minimum number of metastatic cells with the ability to nest in the place of metastasis and a receptivity target organ with a "hospitable" microenvironment. With these premises we can understand that we have a not excessively aggressive or undifferentiated primary tumor, circulating tumor cells that are discarded from the primary rather than actively migrating and one target organ that do not have the appropriate conditions for nesting for these cells.

In Piet Ost's work the factors that predicted survival in patients with metastatic prostate cancer after radiotherapy treatmentwere: PSA doubling time greater than three months before the development of metastasis, presence of less than 3-5 metastases and the pattern of lymph node dissection versus bone [4]. On the other hand, we know from the results of trials such as TAX 327 that the location of these metastases also influences survival, being better for exclusive lymph node and exclusive bone locations than for the combination of both or visceral involvement [10]. With these data we can infer that patients with less those 5 metastases, exclusively in lymph node or bone localization, have a better prognosis and would be the best candidates for treatment with curative intent.

Table 1: Primary therapies and Gleason Scores.

Initial treatment	n
Radiotherapy + ADT	15
Radiotherapy	3
Prostatectomy	3
Prostatectomy + Adjuvant Radiotherapy	10
Prostatectomy + Salvage Radiotherapy	3
Gleason score	
6	13
7	15
8	5
9	1

Table 2: ADT treatment.

Patients	Results
21 Neoadjuvant ADT	13 patients: ADT from primary treatment + neoadjuvant 8 patients: neoadjuvant ADT
13 W/o neoadjuvant ADT	8 patients: ADT from primary treatment 5 patients: Never treated with ADT

Table 3: Results of our series.	
Característica	Resultado
Diagnostic Test Performed	PET-CT (n=32)/CT/BoneScan (n=2)
Relapse	Node (n=24) Bone (n=7) Node + Bone (n=3)
Number of lesions	Bone(n = 11) and Node (n = 69)
2nd relapse	4 patients 2nd relapse (3 node, 1 bone) 1 patient 3rd relapse(node)
SBRTDoseperceived	75 Gy (30 - 112 Gy)
SBRTsesionsreceived	6
Evolution	- Complete response 27 patients (76,5%) - Partial response 6 patients (14,7%) - Deaths 1 (8,8%)
Toxicity	NO (n=30) Mild (n=4)

As previously mentioned, within the name of oligometastatic disease, four stages with different prognostic values are included: oligometastatic disease, oligorrecurrent, oligorregression and induced oligometastases. In our study we have focused on patients who have had recurrent oligometastatic and oligorrecurrent disease.

C.J. Sweeney presented at ASCO 2016 (American society of clinical oncology) their results in the treatment of these patients. He stated that in the United States the annual incidence of oligometastatic disease is 9000 cases. The factors that predict a good treatment response are the presence of maximum 3 metastases and the absence of visceral disease. This subgroup of patients would have median survival of 7 years compared to 3 years presented by the group with highest tumor burden [11]. Vapiwala defined that a good response is: a long time between the primary treatment and the development of metastases, a number of metastases equal or less than 5, and axial lymph node and bone location [11]. In our study, we decided to accept as oligometastatic those patients who had at maximum 5 metastases of exclusive lymph node, exclusive bone and bone and lymph node metastases.

A key point in identifying these patients is the imaging test that we use to diagnose metastasis. Briganti and et al. describe that sensitivity of CT is around 13% and specificity around 96%, with an overall diagnostic precision of 56% in lymph node recurrence diagnosis in PCa. Although CT provides interesting anatomical information, it does not provide advantages to the bone scan in bone metastases diagnosis [12].

Cher et al., relate the total PSA level and its kinetics as predictors of success in detecting metastases on bone scan. They found that it starts to achieve diagnostic rates from 5% with PSA above 40 ng/ml and PSA above 5 ng/ml/year increase this rate in the same way. Overall, sensitivity is 79% and specificity is 82% [13].

Whole body MRI (WB-MRI) offers anatomical and functional information. It shows good information in long bones metastasis but not so good for small and flat bones. Tombal et al. report values of sensitivity and specificity between 98% and 100% for

bone metastases and sensitivity of 77-82% and specificity of 96-98% for lymphadenopathy diagnosis [14].

Umbehr et al. reported a meta-analysis that includes 44 studies with 2293 patients with 84% of sensitivity and 79% of specificity using PET/CT with ¹⁸F-Choline in initial staging [15].

EAU (European association of Urology) clinical guidelines consider CT and bone scan as initial diagnosis of PCa. They reserve PET/CT with ¹⁸F-Choline and WB-MRI use for recurrence or progression stage [16]. Clinical trials have used these tests to evaluate molecules in M0 stages as reference tests. In our experience, we think that they are not adequate to address the selection of these patients, since failure to diagnose metastases would misclassify our patients. This would imply that the therapy that we are going to perform is not going to give them any advantage in survival or delayed progression of the disease. For this reason, and in the absence of approval for the use of ⁶⁸Ga-PSMA-11 PET, ¹⁸F-Choline PET/CT is the most appropriate test for the staging of these patients.

In our center, ¹⁸F-Choline PET/CT was performed in most patients. Only the first patients to undergo the technique were diagnosed with CT and bone scan.

The study by Okunieff and Singh describes that a main predictor of survival in these patients is the presence of five metastases maximum. In this case, they have an overall 5-year survival of 73% compared to 45% of those with more than 5 metastases. For patients who have less than 5 metastases there is an overall 10-year survival of 36% compared to 18% of those with more than 5 metastases. They also show how those patients with pelvic bone metastases have a worse prognosis than those with axial ones [17]. On the other hand, Peter Ost [4] describes that patients with 3 or less metastases have a better survival than those with more than 5. They also describe as a good prognostic factor a long PSA doubling time (greater than 3 months) and the presence of exclusive lymph nodes metastases. In our study we decided to include patients with maximum 5 bone and lymph node metastases.

SBRT is a non-invasive method of administering high doses of radiation (ablative) to a lesion, avoiding the surrounding healthy tissues, thus reducing toxicity. In addition, it provides a greater precision and control of the movement of the tumor. Doses are administered in few fractions but high doses (> 5-6 Gy) (hypofractionation), allowing more efficient treatments. It causes a DNA injury that directly induces apoptosis. It also has an effect on the endothelium, causing vascular collapse that affects the extracellular microenvironment and also it exerts an immunomodulatory effect, by inducing an immune response against the tumor.

Different treatment regimens have been described. Ahmed et al. administer 1 session of 20 Gy for bone lesions and 3 sessions of 16.5 Gy for lymphadenopathy [18]. In our study, we use similar inclusion criteria. Berkovic propose 10 sessions of 5 Gy for patients with a maximum of 3 lymph node or bone metastases. They report 2-years BRFS (biochemical recurrence free survival) in about 50% of patients [19]. In our center, we used an intermediate scheme. We reported good oncological control without high toxicity. Extreme hypofractionation (sessions of at

Table 4: Comparison of the most remarkable series.

Author	N	Follow up (months)	Local control	CSS/OS	Toxicidad
Berkovic	24	24	100%	PFS 2a: 42% OS 2a: 87.5%	GI>G2:3% GU>G2:6%
Ahmed	17	6	100	CSS 1a: 100%	None
Muacevic	40	42	95.5%	OS 18m: 75%	Boneevent
Casamassima	25	30	90%	PFS 2a: 50% OS 2a: 92%	>G1: 0%
Shick	50	31	90%	BPFS 3a: 54%	
Decaestecker	50	24	100%	PFS 2a: 52% OS 2a : 87%	

least 6 Gy), has presented in most series as the best results for the treatment of both bone and lymph node disease.

In the following table (Table 4) we collect the oncological and toxicity results of the most relevant series [1722].

As we can see most of the mean follow-ups do not exceed 2 years. It is difficult to have a longer follow up since this is a new concept and technique that does not have series with longer follow-ups. Although in our case, data is similar to one reported by centers with similar experience.

Although it is not part of this study, we analyzed the influence of progression free survival with ADT. We have not found differences between ADT administrations or not, or whether adjuvant or concomitant ADT was administered to SBRT. The disparity in the indication criteria may have been one of the factors that explain this lack of association.

When we extrapolate the results of studies such as Berkovic's we can observe that SBRT treatment for oligometastatic disease increases the time to castration resistance by delaying the need for ADT [19].

The fact that this is a retrospective study limits the validity of our study since we do not have a control group and the indication criteria treatment is disparate. Additionally, a longer follow-up will allow us to establish whether these clinical differences translate into an impact on the survival of these patients.

CONCLUSIONS

SBRT is a feasible treatment modality for oligometastatic PCa. In this series, patients had low morbidity. Furthermore, evaluation of the efficacy of metastasis-directed therapy in improving clinical outcomes including survival and occurrence of lymph node and bone events is critical and ongoing.

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