

# Radiotherapy of Oligoprogressive Lesions in Castration-Resistant Prostate Cancer: Impact on Second-Generation Hormone Therapy

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## Abstract

**Background:** The therapeutic standard for oligoprogressive prostate cancer resistant to castration is second-generation hormone therapy. This systemic treatment is expensive. There are oligoprogressive lesions accessible to radiotherapy. **Objectives:** To study the impact of radiotherapy of oligoprogressive lesions on the implementation of second generation hormone therapy. **Patients and Methods:** A retrospective study from 2012 to 2020 was carried out. All patients with oligoprogressive prostate cancer who had received radiotherapy on one or more lesions in progression were collated. Survival was calculated using the Kaplan-Meier method. **Results:** 8 patients were treated with stereotactic and conformational radiotherapy between August 2012 and August 2020 in the context of oligoprogressive prostate cancer resistant to castration. The median age at diagnosis of oligoprogression was 73 years with a median PSA level of 3.11 ng/ml. Nine lesions were diagnosed with PET scan PSMA. All the lesions were treated by radiotherapy with different regimens. After a median follow-up of 12.5 months, 7 patients showed a biochemical response to treatment with a median decrease in PSA of 67%. The median survival without clinical or biochemical progression was 7 months. The median survival without the need for further systemic treatment was 9 months. During the follow-up period, six patients received second-generation hormone therapy to treat their relapse, and the other two showed no clinical or biochemical relapse. **Conclusion:** Radiotherapy may be an alternative to delay the introduction of difficult-to-access second-generation hormone therapy.

py in developing countries. A prospective study could validate this therapeutic approach.

## Keywords

Ablative Radiotherapy, Hormone Therapy, Oligometastasis, Prostate, Castration-Resistant Cancer

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## 1. Introduction

Worldwide, prostate cancer is the second most common cancer in men and the fifth most common cause of cancer death in men [1]. Despite the efficacy of local treatments for the primary disease, 35% of patients will develop metastatic disease from their prostate cancer during follow-up, whether discovered at initial diagnosis or at relapse. After an initial phase of sensitivity to castration, the evolution is inevitably towards the establishment of resistance to castration, which leads to a deterioration in the prognosis of the patients [2] [3].

The value of aggressive treatment of all metastatic disease in oligometastatic patients resistant to castration remains debated. There is insufficient evidence to suggest that aggressive management of the entire metastatic disease would delay the initiation of new systemic therapy. There is also no clear evidence of a benefit in terms of recurrence-free survival or overall survival.

We report here the results of patients treated with ablative and conformal stereotactic radiotherapy for oligometastatic progression of castration-resistant prostate cancer. The clinical benefits, in terms of biochemical recurrence-free survival and survival without the introduction of new systemic therapy, are outlined.

## 2. Patients and Methods

### 2.1. Patients

We retrospectively collected data on patients treated in our Institution from August 2012 to August 2020 with ablative and conformal stereotactic radiotherapy for oligometastatic evolution of castration-resistant prostate cancer.

The concept of oligometastatic cancer has evolved since the theory of Halsted *et al.* in 1894. Indeed, Hellman and Weichselbaum identified oligometastasis as a biological intermediate between localised cancer and polymetastatic cancer with the possibility of localised treatment [4]. Oligoprogressive cancer, on the other hand, corresponds to the progression of a limited number of lesions under systemic treatment [5].

Oligoprogressive prostate cancer is defined as a total of three or fewer progressive lesions either at known metastatic sites and/or the occurrence of new metastases and/or local recurrence [6].

Since the concept of Helman *et al.*, numerous studies have suggested that ablative therapy can significantly improve prognosis and even lead to a cure [7] [8]

[9].

Castration resistance has been defined as a significant increase in PSA (prostate specific antigen) verified on 3 consecutive measurements despite effective castration as evidenced by a testosterone level below 50 ng/dl or 1.7 nmol/l [10].

PSA is measured during surveillance of prostate cancer patients every 6 months until 5 years after local treatment.

Patients who were treated with second-generation hormone therapy prior to radiotherapy and/or whose hormone therapy was performed at most one week after localized ablative therapy were excluded.

## 2.2. Diagnosis of Oligoprogression

PSMA photon emission computed tomography (PSMA PET) imaging was used to identify the oligoprogressive lesion(s).

## 2.3. Treatment

All progressive lesions visible on imaging were treated with stereotactic or conformal radiotherapy with ablative intent, using one of the following hypofractionated regimens:

- 10 Gy × 3 fractions.
- 4 Gy × 5 fractions.
- 12 Gy × 3 fractions.
- 23 Gy × 2 fractions.

## 2.4. Statistical Analysis

The statistical analyses were carried out using SPSS 25 software. (IBM, U.S.A).

For each patient, we identified the criteria of clinical interest (initial stage, existence of local treatment of the primary, PSA level at the time of castration-resistant oligoprogression) and calculated the clinical or biochemical progression-free survival as well as the survival without introduction of a new systemic treatment.

Progression-free survival (PFS) was calculated from the last day of radiotherapy treatment to clinical and/or biochemical progression.

Survival without the introduction of new systemic therapy was calculated from the last day of treatment to the date of initiation of new systemic therapy with 2nd generation hormone therapy.

## 3. Results

From August 2012 to August 2020, 8 patients were treated with ablative and conformal stereotactic radiotherapy at Gustave Roussy for oligoprogression of castration-resistant prostate cancer.

### 3.1. At the Time of Initial Diagnosis (Table 1)

The median age was 70 years. The median PSA level at initial diagnosis was 25.1

ng/ml. In 3 patients, the disease was immediately metastatic (37.5% of cases). Local treatment of the primary was performed in 6 patients (75%). This consisted of radiotherapy in 3 patients and surgery followed by salvage radiotherapy in 3 patients. Hormonal castration was performed in all patients.

**Table 1.** Characteristics of patients with castration-resistant prostate cancer in oligoprogression.

At the time of diagnosis	Staff (percent)
Median age, year	70 (56 - 79)
median PSA, ng/ml	25.1 (4.9 - 3609)
Metastatic disease, n (%)	3 (37.5)
Local treatment of the primary disease, n (%)	6 (75)
Androgenic castration, n (%)	8 (100)
At the time of oligoprogression	
Median age, year	73 (60 - 81)
median PSA, ng/ml	3.11 (2.5 - 43.8)
Diagnostic imaging, n (%)	
PET-CT (PSMA/Choline)	8 (100)
Conventional imaging	1 (12.5)
Number of progressive lesions, n (%)	
1	7 (87.5)
2	1 (12.5)
Types of progressive lesions, n (%)	
Bone	8 (87.5)
Local relapse	1 (12.5)
Treatment, n (%)	
Radiotherapy	8 (100)
Radiotherapy technique	
Stereotaxis	7 (77.77)
3D	2 (22.23)
Fractionation, n lesion	
10 Gy × 3 fractions	6 (1)
4 Gy × 5 fractions	1 (1)
12 Gy × 3 fractions	1 (1)
23 Gy × 2 fractions	1(1)

### 3.2. At the Time of Diagnosis of Oligoprogressive Castration-Resistant Prostate Cancer (Table 1)

The median age at diagnosis of oligoprogression was 73 years with a median PSA level of 3.11 ng/ml. Diagnosis of progression was performed by PSMA PET. One patient had an initial CT scan before PSMA PET. Imaging had revealed 9 lesions, two of which were in one patient. There were 8 bone lesions (87.5%) and 1 local relapse (12.5%). All lesions were treated by external radiotherapy, 7 of which were treated by stereotaxis (77.77%) and 2 by three-dimensional conformal technique (22.23%). Various treatment regimens were used: 20 Gy in 5 fractions on one lesion, 30 Gy in 3 fractions on six lesions, 36 Gy in 3 fractions on one lesion, 46 Gy in 2 fractions on one lesion with no side effects. Systemic treatment was continued before, during and after radiotherapy. Seven patients (87.5%) had a single line of hormone therapy and one patient had Docetaxel in addition to hormone therapy.

### 3.3. Oncological Outcomes after Radiotherapy of Oligoprogressive Castration-Resistant Prostate Cancer (Table 2)

The median follow-up of patients after ablative or conformal stereotactic radiotherapy was 12.5 months (min 5; max 93). Seven patients showed a biochemical response to treatment with a median decrease in PSA of 67%. One patient was non-responder to treatment with a rise in PSA following radiotherapy. Median progression-free survival (PFS) was 7 months (min 2; max 75) (**Figure 1**). Median survival without the need for further systemic therapy was 9 months (min 3; max 75) (**Figure 2**). During the follow-up period, six patients received second-generation hormone therapy to treat their relapse, and the remaining two did not show clinical or biochemical relapse.

## 4. Discussion

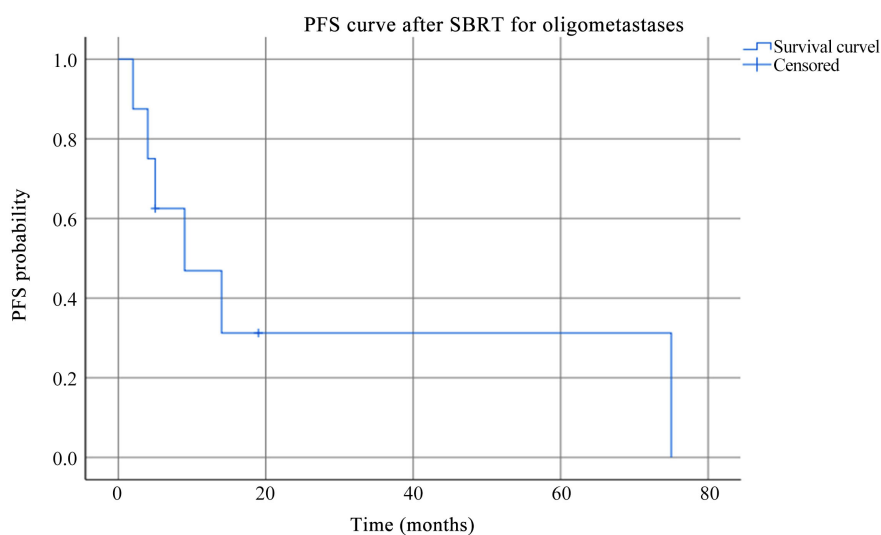
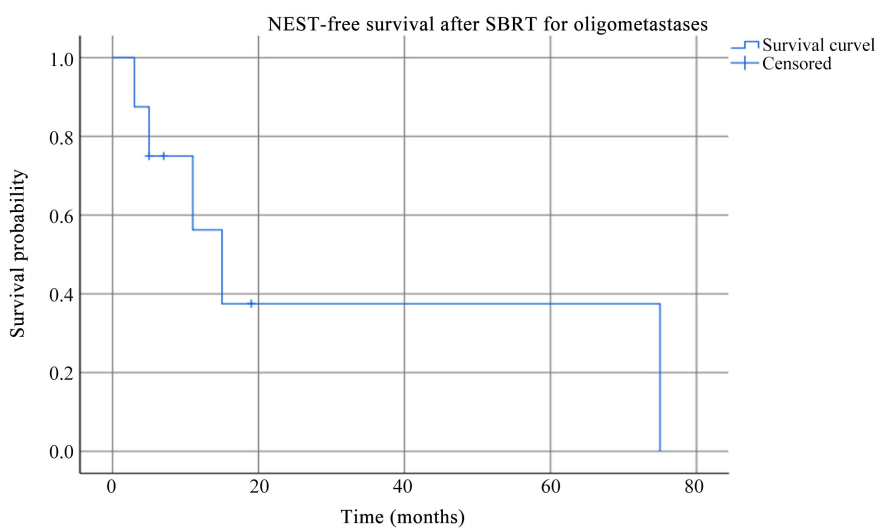
The prognosis of oligometastatic prostate cancer is approximately equal to that of non-metastatic prostate cancer [11]. However, there is a difference in survival depending on the number and location of metastases. Indeed, the SEER (Surveillance, Epidemiology, and End Results -Medicare insurance program-linked database) study showed that in terms of overall survival and progression-free survival, patients with a single metastatic site had a better prognosis. It also showed that lymph node sites were better than bone sites [12].

In our study, we found 9 progressive lesions, 8 of which were bone lesions and 1 local relapse.

The diagnostic methods are diverse but have different sensitivities depending on the PSA level. For a PSA of less than 7 ng/ml, scintigraphy has almost no sensitivity. Dynamic examinations such as choline PET and PSMA PET allow the diagnosis of recurrence and micro metastases (respectively 90% and 97% for a PSA level above 2 ng/ml) [13] [14]. The median PSA level at oligoprogression was 3.11 ng/ml. All oligoprogressive lesions were diagnosed by PET-PSMA.

**Table 2.** Oncological outcomes after radiotherapy of oligoprogressive castration-resistant prostate cancer.

Response n (%)	
Yes	7 (87.5)
No	1 (12.5)
Need for 2nd generation hormone therapy after radiotherapy, n (%)	6 (75)
Median follow-up (months)	12.5 (5 - 93)
Median survival without 2nd line hormone therapy (months)	9 (3 - 75)
Median progression-free survival (months)	7 (2 - 75)

**Figure 1.** Progression-free survival curve after radiotherapy of oligoprogressive castration-resistant prostate cancer.**Figure 2.** Survival curve without second generation hormone therapy after radiotherapy of oligoprogressive castration-resistant prostate cancer.

In case of oligoprogression, there are different treatment strategies [15]:

- modification of systemic treatments;
- continuation of current systemic therapy if progression is considered minimal;
- management of metastatic progression with radical local treatment, such as stereotactic radiotherapy, to extend the time frame without modification of systemic treatments.

Our approach was to treat all oligoprogressive lesions radically with stereotactic and conformal radiotherapy while retaining systemic treatment.

The natural history of metastatic prostate cancer shows that the clinical benefit of systemic treatment is 2 - 3 years. Switching to second-generation hormone therapy when oligoprogression of castration-resistant prostate cancer occurs is the standard of care. The use of radiotherapy in oligoprogression is not a defined standard, but specialists use it. Radiotherapy is mainly used for bone or lymph node lesions found on dynamic examinations (choline PET, PSMA PET). The fractions and doses vary from one study to another [16]. A retrospective, multi-centre observational study showed a progression-free survival after radiotherapy of 12.3 months over a median follow-up of 30.7 months [17]. The study by Charlien *et al.* found a progression-free survival requiring second-generation hormone therapy of 10 months after a follow-up of 18 months [6]. In our study, after a median follow-up of 12.5 months, we found a progression-free survival requiring second-generation hormone therapy of 9 months (6 patients). The results in terms of survival without second-generation hormone therapy are similar to those of Charlien *et al.* [6]. The role of radiotherapy on oligoprogressive lesions in oligoprogressive prostate cancer has yet to be defined because the studies conducted to date are insufficient [18].

The limitations of our study are that it is a retrospective study with a very small number of patients. Nevertheless, the results confirm the very rare poor data in the literature.

## 5. Conclusions

The standard treatment for oligoprogressive castration-resistant prostate cancer is second-generation hormone therapy.

However, this systemic treatment is not available in all countries, especially in the developing world.

Radiotherapy may be an alternative and a prospective study could validate this therapeutic approach.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## Abbreviations

SBRT: stereotactic radiotherapy

NEST: second-generation hormone therapy

PFS: progression-free survival

PSA: prostate specific antigen

Gy: Gray

PET-PSMA: positron emission tomography-Prostate specific membrane antigen