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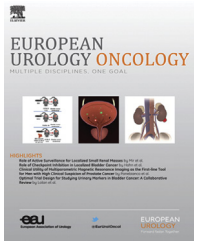

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Progression-directed Therapy for Oligoprogression in Castration-refractory Prostate Cancer

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Abstract

In metastatic castration-refractory prostate cancer (mCRPC), state-of-the-art treatment consists of androgen biosynthesis inhibition (abiraterone), inhibition of the androgen receptor (enzalutamide), chemotherapy, or radium-223 in combination with androgen deprivation therapy (ADT). A subgroup of these patients show oligoprogression, with the progression of only a limited number of metastatic spots, while all other metastases remain controlled by ongoing systemic therapy. In a bi-institutional retrospective study, we tested the hypothesis that progression-directed therapy (PDT) targeting oligoprogressive lesions might defer the initiation of next-line systemic treatment (NEST). A total of 30 patients were diagnosed with mCRPC and experienced oligoprogression, defined as a total of three or fewer progressive lesions either at known metastatic sites and/or the appearance of new metastasis and/or local recurrence. All patients were under active ADT with or without second-line systemic treatment. All patients received PDT targeting the oligoprogressive lesions, while ongoing systemic treatment was maintained. There was median NEST-free survival of 16 mo (95% confidence interval [CI] 10–22) and progression-free survival of 10 mo (95% CI 6–15) with only minor radiotherapy- or surgery-related toxicity. These findings encourage further prospective trials.

Patient summary: In patients with metastatic castration-refractory prostate cancer, surgical treatment or high-dose radiation therapy directed to only the limited number of progressive metastatic spots, while all other metastases remained controlled by ongoing systemic therapy, led to substantial postponement of next-line systemic treatment in our study.

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In metastatic hormone-sensitive prostate cancer (mHSPC) the sensitivity to castration will eventually disappear due to selection of castration-resistant clones, so the patient progresses to metastatic castration-refractory prostate cancer (mCRPC). Median survival in mCRPC is approximately 35 mo [1], depending on different prognostic factors and the use of second- and third-line systemic treatment regimens, which come with a non-negligible financial cost and toxicity [2]. Clinical and iconographic progression (and to a lesser extent biochemical progression) traditionally implies a switch to next-line systemic treatment (NEST). A subgroup of mCRPC patients presents with oligoprogression, defined as the appearance or progression of a limited number (typically a maximum of 3) of lesions while the

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majority of lesions are controlled by the ongoing systemic therapy [3]. This heterogeneous response to treatment reflects the heterogeneity of subclones within the different metastatic spots [4]. When oligoprogression occurs, only a minor fraction of the total disease burden progresses. The majority of the total disease burden is still sensitive to the ongoing systemic treatment. By using progression-directed therapy (PDT) targeting these oligoprogressive lesions, patients can possibly remain on their current systemic therapy, thereby delaying the need for NEST [5,6].

For this retrospective study, we identified patients from two institutional databases fulfilling the following criteria: all patients received PDT on all the oligoprogressive lesions, either metastasis-directed therapy (MDT) of stereotactic body radiation therapy (SBRT) or metastasectomy, as well as fractionated radiotherapy for metastasis or local recurrence. In our study, oligoprogression was defined as the appearance or progression of up to three lesions as metastatic spots (N, M1a, M1b, and/or M1c) and/or local relapse/disease in patients with mCRPC while under treatment with androgen deprivation therapy (ADT) with or without other systemic treatments. CRPC was defined as a rise in prostate-specific antigen (PSA) with testosterone level below 50 ng/dl, with proven documentation of testosterone serum castrate levels in all cases. The study was approved by the ethics committee of University Hospitals Leuven (S61314) and was conducted according to the Declaration of Helsinki. In total, 30 patients fulfilled the inclusion criteria and presented with 45 oligoprogressive lesions. Treatment of metastatic disease consisted of SBRT ($n = 18$), metastasectomy ($n = 2$), or fractionated radiotherapy ($n = 7$). Treatment of locoregional progression consisted of fractionated radiotherapy ($n = 3$). We calculated the time to NEST from the last day of radiotherapy or the day of surgery until the start of NEST. Progression-free survival (PFS) was calculated from the date of the multidisciplinary oncological board meeting on which the decision between PDT and NEST was made until clinical or biochemical progression in the case of PFS. At the time of initial diagnosis of prostate cancer, 47% of the patients had upfront bone metastases, and 53% received ADT as part of the initial treatment. Primary treatment consisted of surgery ($n = 4$), radiotherapy ($n = 5$), a combination of both ($n = 15$), or ADT only ($n = 6$). Table 1 summarizes the patient and disease characteristics.

The imaging used to define the oligometastatic setting was, as expected, heterogeneous. Conventional imaging with computed tomography (CT) scan and bone scans were used in 11 patients, choline positron emission tomography (PET)/CT in three, prostate-specific membrane antigen PET/CT in 14 (in combination with other imaging for 2 patients), and magnetic resonance imaging in two. The therapeutic strategy was discussed in multidisciplinary board meetings. In the case of SBRT, patients were treated to a normalized isoeffective dose in 2-Gy fractions (NID_2) of between 78 and 142.8 Gy, delivered in three to five fractions. Fractionated therapy consisted of 13×3 Gy or 5×4 Gy for metastatic progression, and 35×2.2 Gy, 25×2.64 Gy, or 16×3.65 Gy for locoregional relapse. The two metastasectomy sites were one perirectal metastatic mass and one solitary lesion in the lower lobe of the lung. An overview of the disease span and treatments is shown in a swimmers plot in Fig. 1. Over median follow-up of 18 mo (interquartile range 8–25) the median NEST-FS was 16 mo (95% confidence interval [CI] 10–22) and PFS was 10 mo (95% CI 6–15). The group receiving SBRT or metastasectomy ($n = 20$) had NEST-FS of 21 mo (95% CI 14–28). At the time of last follow-up, 87% of the patients were still alive. Kaplan-Meier survival curves for NEST-FS are presented in Fig. 2A,B. Toxicity was scored according to the Common Terminology Criteria for Adverse Events scoring system for radiotherapy and the Clavien-Dindo classification for surgery. Treatment-related toxicity was minor, with three patients experiencing grade 1 toxicity, consisting of acute gastrointestinal (GI) toxicity ($n = 2$), acute genitourinary (GU) toxicity ($n = 1$), and fatigue ($n = 1$). One patient developed grade 2 acute GI

Table 1 – Patient characteristics.

Parameter	Result
At initial PC diagnosis	
Median age, yr (IQR)	64 (57–69)
Median prostate-specific antigen, ng/ml (IQR)	12 (7–17)
Risk features, *n* (%)	
Intermediate	5 (17)
High	10 (33)
Unknown	1 (3)
Metastatic disease, *n* (%)	14 (47)
Metastatic burden for patients with mPC (*n*) [a]	
Low	13
High	0
Unknown	1
Local treatment of the primary tumor, *n* (%)	24 (80)
Androgen deprivation therapy, *n* (%)	16 (53)
Median time to mPC for patients with initial nmPC, mo (IQR)	60 (24–95)
At oligoprogression	
Median age, yr (IQR)	70 (66–75)
Median prostate-specific antigen, ng/ml (IQR)	3 (1–11)
Median time on systemic therapy, mo (IQR)	33 (20–50)
Number of progressive lesions, including LCR, *n* (%)	
1	18 (60)
2	9 (30)
3	3 (10)
Type of lesion, *n* (%)	
Lymph node	5 (17)
Bone	20 (66)
Lymph node + bone	1 (3)
LCR	3 (10)
Lung	1 (3)
Toxicity, *n* (%)	
Grade 1	3 (10)
Grade 2	1 (3)
Grade 3	1 (3)
Grade 4	0
Grade 5	0
Outcomes	
Median follow-up, mo (IQR)	18 (8–25)
Median progression-free survival, mo (95% CI)	10 (6–15)
Median NEST-free survival, mo (95% CI)	
Overall	16 (10–22)
Stereotactic body radiation therapy only	21 (14–28)

PC = prostate cancer; mPC = metastatic PC; nmPC = nonmetastatic PC; IQR = interquartile range; LCR = local recurrence; NEST = next-line systemic treatment; CI = confidence interval.
[a] Metastatic burden was classified as low or high according to the CHAARTED/STAMPEDE criteria.

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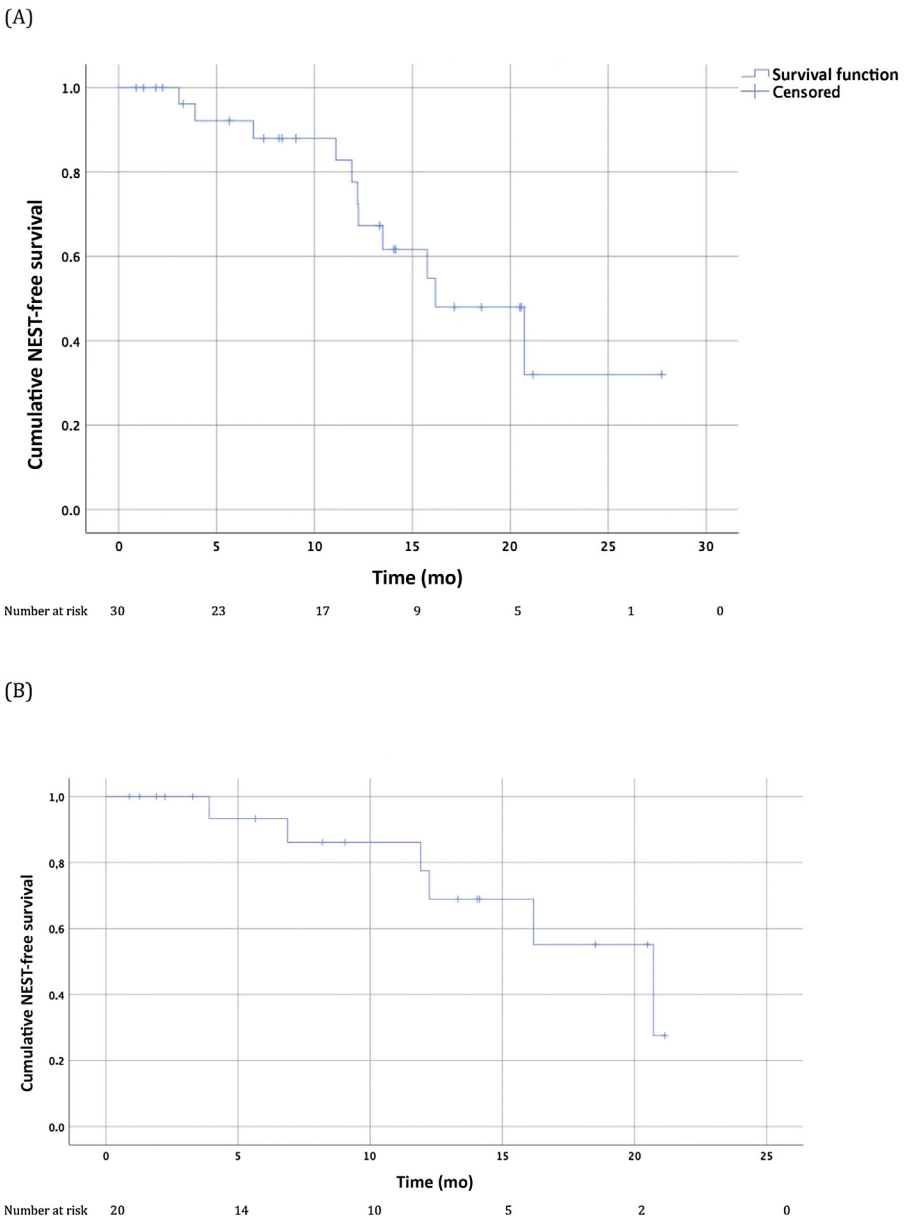

Fig. 1 – Next-line systemic treatment–free survival (NEST-FS) for (A) the progression-directed therapy group and (B) the metastasis-directed therapy group treated with stereotactic body radiation therapy or metastasectomy.

toxicity and one patient had late grade 3 GU/GI toxicity (due to local treatment).

Data on PDT in the setting of oligoprogression in mCRPC are scarce but emerging. A case report demonstrated the potential of SBRT as an additional tool in long-term control of oligoprogressive disease in CRPC, while the mainline systemic therapy could be preserved [7]. In a multicenter retrospective analysis [5], a subset of patients experienced oligoprogressive CRPC while on ADT. For these patients, initiation of second-line systemic therapies could be postponed for 22 mo when the oligoprogressive lesions were treated with SBRT, which closely resembles our results, although patients receiving second-line systemic treatment were allowed in our series. Others reported on SBRT for oligometastatic disease in both mHSPC and CRPC [8,9], with only limited information on CRPC patients. Tran et al [10] observed 1-yr NEST-FS of 30% in a group of 17 CRPC patients. Ongoing prospective trials are investigating the role of SBRT for oligometastatic CRPC (NCT02192788, NCT02759783, NCT02816983, and NCT01859221) and others are addressing the combination of SBRT and second-line hormone therapy (NCT03449719 and NCT02685397).

This trial has several limitations inherent to its retrospective design. Patient characteristics and the imaging and treatment modalities are heterogeneous. Nevertheless, the NEST-FS of 16 mo (and 21 mo for the SBRT/metastasectomy group) is hypothesis-generating. In terms of health

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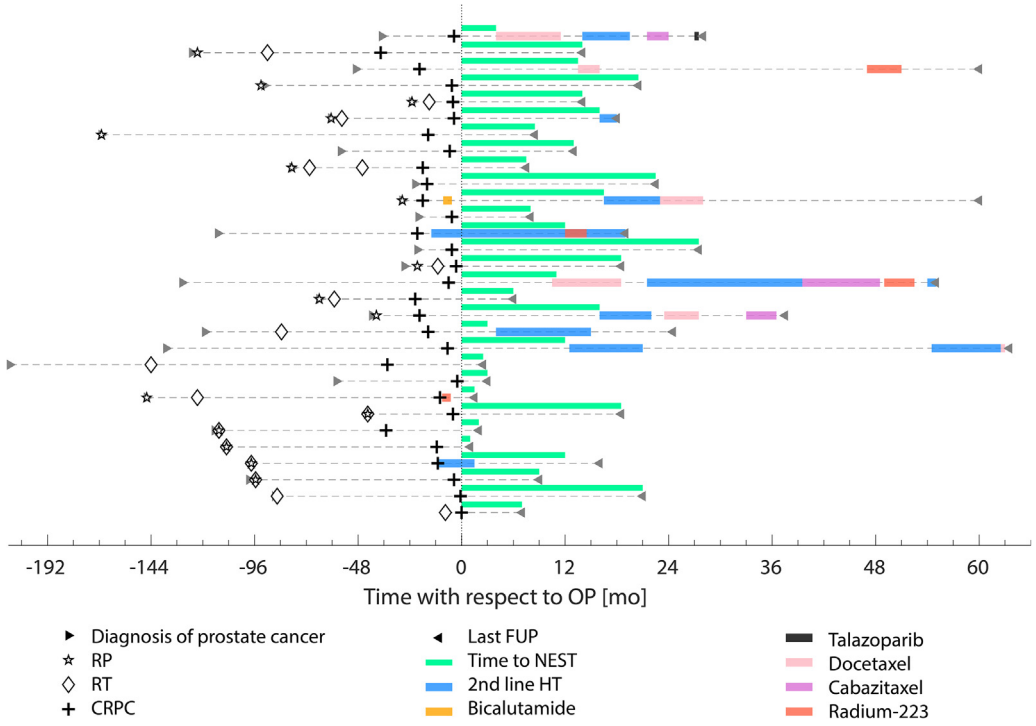

Fig. 2 – Swim lanes illustrating the therapies before and after OP diagnosis. RP = radical prostatectomy; RT = radiation therapy; CRPC = castration-refractory prostate cancer; FUP = follow-up; NEST = next-line systemic treatment; HT = hormone therapy; OP = oligoprogression (day of surgery or last day of RT was used as time zero for OP).

economics, PDT has the potential to significantly reduce costs. Properly designed prospective trials are needed in which the role of the new imaging modalities needs to be addressed in comparison with conventional imaging. Endpoints such as NEST-FS are subject to the decision made by the multidisciplinary board and clear prespecified criteria for initiation of NEST need to be established; for example, a PSA doubling time of <4 mo could imply a need for subsequent systemic therapy. Our research group has initiated a prospective phase 2 trial on the basis of the encouraging results from this investigation.

Author contributions: Charlien Berghen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Berghen, Joniau, De Meerleer.
Acquisition of data: Berghen, De Meerleer.
Analysis and interpretation of data: Berghen, Joniau, De Meerleer.
Drafting of the manuscript: Berghen, Joniau, Ost, Poels, Everaerts, Decaestecker, Haustermans, Devos, De Meerleer.
Critical revision of the manuscript for important intellectual content: Berghen, Joniau, Ost, Poels, Everaerts, Decaestecker, Haustermans, Devos, De Meerleer.
Statistical analysis: Berghen, De Meerleer.
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Supervision: Berghen, Joniau, De Meerleer.
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