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ORIGINAL ARTICLE – CANCER RESEARCH

Predictive factors for survival outcomes of oligometastatic prostate cancer patients treated with metastases-directed therapy: a recursive partitioning-based analysis

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Abstract

Purpose The aim of the present study was to provide predictive factors for survival outcomes of oligometastatic prostate cancer (PC) patients treated with stereotactic body radiation therapy (SBRT) as a metastases-directed therapy (MDT).

Methods In this cohort study, endpoints included overall survival (OS), progression-free survival (PFS), distant progression-free survival (DFS) and local control of treated metastases (LC). The binary classification tree approach with recursive partitioning analysis (RPA) was applied to stratify the patients into risk groups based on OS, PFS and DPFS; for each endpoint, disease-free interval (DFI) was calculated. We included patients with synchronous or metachronous metastases from prostate adenocarcinoma treated with SBRT.

Results 119 Metastases were treated with SBRT in 92 patients. Median follow-up was 22.2 months. Rates of OS at 1 and 3 years were 96.9% and 88.0%, while DPFS was 51.9% and 20.9%. Recursive partitioning analysis identified three prognostic classes for OS: Class 1: castration-sensitive patients (3 years OS 95%); Class 2: castration-resistant patients with low-intermediate risk NCCN disease (3 years OS 88.8%); Class 3: castration-resistant patients with high-risk NCCN disease (3 years OS 76.9%). Regarding DPFS, RPA divided patients into two classes, according to a cutoff value of DFI of 34 months (3 years PFS of 28.7% vs 5.8%). Three classes were identified for DPFS: Class 1: DFI < 34 months (3 years DPFS 9.1%); Class 2: DFI > 34 months and high-risk NCCN PC (3 years DPFS 21%); Class 3: DFI > 34 months and low-intermediate risk NCCN disease (3 years DPFS 60.2%).

Conclusion Oligometastatic PC represents nowadays a setting of particular interest in which local ablative therapies play a decisive role. In the present study, we recognized the importance of DFI, together with NCCN class risk, to predict the risk of new metastases after SBRT in oligometastatic PC.

Keywords SBRT · Stereotactic body radiation therapy · Radiotherapy · Oligometastases · Prostate cancer · Oligometastatic · PSA kinetics

Introduction

Prostate cancer (PC) represents the second most common cancer in men worldwide (Ferlay et al. 2019) with clear evidence of benefit from radiotherapy (RT) and surgery on localized disease (Häggman et al. 2002; Lund et al. 2008; Hamdy et al. 2016). Advanced PC can often present as an oligometastatic disease (De Bruycker et al. 2017), defined as an intermediate state between localized and widespread disease (Hellman and Weichselbaum 1995). Oligometastatic PC is characterized by the presence of a maximum of 3–5 metastases in up to 2 sites. Most common sites of metastases from PC are bones and lymph nodes. While systemic

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therapies, including standard androgen deprivation therapy (ADT), chemotherapy and new-generation hormonal therapies, represent the standard of care for multimetastatic disease, the role of metastases-directed therapy (MDT) in case of limited number of metastases remains debated. This is caused by the paucity of prospective and randomized trials, even if limited experiences have been reported (Ost et al. 2015, 2016; Muacevic et al. 2013; Tran et al. 2018). The main benefits from MDT in PC are potentially: (1) increasing the time of freedom from systemic therapy in naïve patients; (2) delaying the onset of new lines of systemic therapy in patients with ongoing treatment.

Considering the lack of a standardized definition of oligometastatic disease, selection of patients candidate to MDT needs to be clarified. The aim of the present study was to provide predictive factors for survival outcomes of oligometastatic PC patients treated with stereotactic body radiation therapy (SBRT) as an MDT.

Materials and methods

Study population

We included in this monocentric analysis patients with diagnosis of prostate adenocarcinoma, treated with radical RT or surgery with or without adjuvant/salvage RT of primary tumors, with diagnosis of synchronous or metachronous metastases treated with SBRT. The multidisciplinary uro-oncology team approved all treatments. The local ethics committee approved the analysis. Patients were candidate to SBRT if a maximum of 5 metastases up to 5 cm were diagnosed in 1–2 organs. Concomitant systemic treatment was allowed. All patients were staged with 11c-choline PET or 68ga-PSMA PET scan. The study was conducted in accordance with the Good Clinical Practice guidelines, the ethical principles of the Declaration of Helsinki and local regulations.

Techniques of radiotherapy

Patients were simulated with CT scan, co-registered with PET scan. All patients were positioned supine with a thermoplastic mask. The clinical target volume (CTV) was equal to gross tumor volume (GTV) and an isotropic margin of 5–10 mm, depending on disease site and dimensions, was added to CTV to obtain the planning target volume (PTV). All patients were treated with volumetric modulated arc therapy technique. Patient's position was evaluated daily with cone-beam CT imaging before each treatment session. Patients treated with systemic therapy underwent SBRT in case of oligoprogression.

Biological effective dose (BED) was calculated to compare different schedules of RT. The linear quadratic model was used for calculation as follows (Park et al. 2008):

$$\mathrm{BED(Gy)} = \text{dose per fraction} \times \text{number of fractions} \times \left(1 + \frac{\text{dose per fraction}}{\alpha/\beta}\right).$$

BED was calculated for prostate with a α/β of 3.

Response assessment

First evaluation was performed 3 months after SBRT and then every 3 months for the first year and every 6 months from the second to the fifth year. Clinical evaluation and PSA values were obtained for every visit, while diagnostic imaging was planned according to physician choice or in case of three consecutive increases in PSA levels. Tumor response was classified according to the European Organization for Research and Treatment of Cancer Response Evaluation Criteria In Solid Tumours (EORTC-RECIST) criteria version 1.16. PET Response Criteria in Solid Tumors (PERCIST) were used to evaluate metabolic response in patients who underwent PET scan for restaging.

Statistical analysis

End points of the present study included overall survival (OS), progression-free survival (PFS), local control of treated metastases (LC), and distant progression-free survival (DPFS). Overall survival was calculated from SBRT to either death or last follow-up. PFS was defined as the time from SBRT to the evidence of infield or outfield progression or increase of PSA. Distant progression-free survival was defined as the time from SBRT to the onset of new metastases. Local control was defined as the time from the beginning of SBRT to the infield progression or last follow-up. Univariate analysis was performed with the log-rank test, and Cox proportional hazards regression was used to estimate hazard ratios (HR). Multivariable Cox regression analysis was performed to evaluate the association between clinical factors and survival, with a significance level of $p < 0.05$.

Variables included in the analysis were age, performance status (PS), initial PSA (iPSA), Gleason score, NCCN class risk, disease-free interval (DFI), time to diagnosis of metastases, time from biochemical relapse to diagnosis of metastases (months), number of treated metastases, number of treated sites, PSA pre-RT, PSA doubling time (PSAdt), PSA velocity (PSAv), type of imaging before RT, previous ADT, previous chemotherapy, systemic lines before RT, prior new generation hormonal therapy, castration resistance,

classification of disease according to the CHARTEED criteria (Sweeney et al. 2015) and LATITUDE criteria (Fizazi et al. 2017).

The binary classification tree approach with recursive partitioning analysis (RPA) was applied to stratify the patients into risk groups based on OS and DPFS. We performed RPA for the whole population according to the castration sensitivity vs. resistance. Pre-treatment characteristics were included in RPA to identify prognostic classes (Breiman et al. 1984). Statistical calculations were performed using STATA, version 14.

Results

From 2009 to 2018 a total 119 metastases were treated with SBRT in 92 patients. Patients' characteristics and treatments' details are summarized in Table 1. Median age was 70.9 years (49.8–82.9) and PS was 0 for the majority of patients (59, 64.1%). Gleason score sum was 8 and 9 in 13 (14.1%) and 30 (32.6%) patients, respectively. Median DFI was 33.9 months (0–186.6) and median time to diagnosis of metastases was 41 months (0–207.3). Patients were treated on 1 (61, 66.3%), 2 (27, 29.3%) or 3 (4, 4.4%) metastases. Median PSA value before SBRT was 2.03 ng/ml, while median PSAdt and PSAv were 4 months and 2.64 ng/ml/year, respectively. Disease was classified as high volume/risk in 78 (84.8%) and 49 (53.3%) patients according to the CHARTEED and LATITUDE criteria, respectively. Thirty-one (33.7%) patients were considered castration resistant when treated with SBRT. ADT was administered before SBRT in 43 (46.7%) patients and chemotherapy was administered in 10 (10.9%) patients. Eleven (12%) patients received abiraterone or enzalutamide. Median time from diagnoses of metastases to SBRT was 2.21 months (0.2–7.61). The total delivered dose ranged from 18 to 60 Gy and median dose was 42 Gy, in 2–8 fractions. Median BED was 157.5 Gy (66.6–240).

The median follow-up was 22.2 months (3–114). Kaplan–Meier curves for OS, PFS, DPFS and LC are shown in Fig. 1. At the time of the analysis, 79 patients were alive, with a median OS of 91.6 months (3–114). Rates of OS at 1 and 3 years were 96.9% (95% CI 88.5–99.2) and 88.0% (95% CI 74.8–94.5).

At univariate analysis, predictive factors for OS were: Gleason score (HR 3.28, 95% CI 1.70–6.35; $p=0.000$), NCCN class risk (HR 12.93, 95% CI 1.67–100.11; $p=0.014$), use of ADT (HR 10.24, 95% CI 1.31–79.52; $p=0.026$) or chemotherapy (HR 4.69, 95% CI 1.16–18.9; $p=0.030$) before SBRT, castration resistance (HR 12.88, 95% CI 1.66–99.87; $p=0.014$), and high volume/risk disease according to LATITUDE criteria (HR 4.95, 95% CI 1.32–18.60; $p=0.018$). At multivariable analysis, only previous ADT impacted on OS (HR 1.16, 95% CI 7.55–17.9; $p=0.000$).

Median PFS was 9.4 months (2–49.6). PFS rates at 1 and 3 years were 42.8% (95% CI 31.5–53.6) and 16.7% (95% CI 8.2–27.7). At univariate analysis, DFI (HR 0.99, 95% CI 0.98–0.99; $p=0.043$), number of treated metastases (HR 1.81, 95% CI 1.14–2.89; $p=0.012$), PSAv (HR 1.01, 95% CI 1.00–1.02; $p=0.037$), previous chemotherapy (HR 2.66, 95% CI 1.25–5.42; $p=0.010$) and number of systemic lines before SBRT (HR 1.44, 95% CI 1.05–1.98; $p=0.022$) were significantly associated with PFS. However, none of the factors continued to be significant at multivariable analysis (Tables 2, 3, 4, 5).

In detail, 55 patients developed new metastases after SBRT with a median DPFS of 13.0 months (2–54.3). Rates of DPFS at 1 and 3 years were 51.9% (95% CI 40.1–62.4) and 20.9% (95% CI 10.6–33.7). At univariate analysis, age (HR 0.50, 95% CI 0.26–0.95; $p=0.037$), DFI (HR 0.98, 95% CI 0.98–0.99; $p=0.004$), time to diagnoses of metastases (HR 0.99, 95% CI 0.98–0.99, $p=0.007$), PSAv (HR 1.01, 95% CI 1.00–1.02; $p=0.017$), previous ADT (HR 1.80, 95% CI 1.05–3.11; $p=0.033$), previous chemotherapy (HR 2.79, 95% CI 1.34–5.77; $p=0.006$), number of systemic lines before SBRT (HR 1.59, 95% CI 1.15–2.19; $p=0.005$) and castration resistance (HR 1.74, 95% CI 1.01–2.97; $p=0.043$) were statistically associated with DPFS. At multivariable analysis, only PSAv remained predictive factor (HR 1.01, 95% CI 1.00–1.02, $p=0.049$).

Progression of treated metastases was diagnosed in ten patients. Median LC was not reached. LC rates at 1 and 3 years were 90.9% (95% CI 81.8–95.6) and 85.5% (95% CI 74.4–92.0). At univariate analysis, none of the analyzed factors was significantly affecting LC.

Applied to the whole population, RPA identified three prognostic classes for OS (Fig. 2). Class 1 was represented by castration-sensitive patients, with 3 years OS of 95% (95% CI 69.4–99.2%). Class 2 included castration-resistant patients with low-intermediate risk disease (3 years OS of 88.8%, 95% CI 43.3–98.3). Castration-resistant patients with high-risk disease were classified as class 3, with 3 years OS of 76.9% (95% CI 48.9–90.8). The difference among the three classes was statistically significant in terms of OS ($p=0.0003$). Based on Cox proportional hazards with class 1 as the reference, HR for classes 2 and 3 were 3.18 (95% CI 0.19–51.18, $p=0.414$) and 18.54 (95% CI 2.36–145.36; $p=0.005$), respectively.

In terms of DPFS, RPA divided the patients into three classes (Fig. 2). Class 1 included patients with DFI < 34 months (3 years DPFS of 9.1%, 95% CI 1.9–23.1), class 2 included patients with DFI ≥ 34 months and high-risk disease (3 years DPFS of 21%, 95% CI 4–46.7), and Class 3 included patients with DFI ≥ 34 months and

Table 1 Patient's and treatment's characteristics

	N (%) 92 pts, 119 lesions
Age median (range)	70.9 (49.8–82.9)
≤65	19 (20.6%)
> 65	73 (79.4%)
PS	
0	59 (64.1%)
1	25 (27.2%)
2	8 (8.7%)
Initial PSA, median (range) ng/ml	10.2 (3.7–148)
Gleason score	
3+3	6 (6.5%)
3+4	21 (22.8%)
4+3	22 (23.9%)
4+4	13 (14.1%)
4+5	19 (20.6%)
5+4	11 (11.9%)
NCCN class risk	
Low	3 (3.3%)
Intermediate	44 (47.8%)
High	45 (48.9%)
Initial treatment	
Surgery	70 (76.1%)
HIFU	6 (6.5%)
ADT	8 (8.7%)
Radiotherapy	8 (8.7%)
Time to biochemical relapse, median months (range)	33.9 (0–186.6)
Time to diagnosis of metastases, median months (range)	41 (0–207.3)
Time from biochemical relapse to diagnosis of metastases, median (range)	1 (0–129.8)
Number of total treated metastases	
1	61 (66.3%)
2	27 (29.3%)
3	4 (4.4%)
Number of treated lymph nodes	
1	44 (47.8%)
2	22 (23.9%)
3	4 (4.3%)
Number of treated bone metastases	
1	20 (21.7%)
2	2 (2.2%)
Number of treated lung metastases	
1	3 (3.3%)
Number of interested sites	
1	89 (96.7%)
2	3 (3.3%)
PSA pre-radiotherapy, median (range)	2.03 ng/ml (0.03–58.2)
PSA doubling time, months median (range)	4 (1–62)
PSA velocity, median (range)	2.64 (0.06–113.1) ng/ml/years
Imaging before radiotherapy	
Choline PET	81 (88.1%)
PSMA-PET	11 (11.9%)
CHARTEED criteria	
Low volume	14 (15.2%)

Table 1 (continued)

	N (%) 92 pts, 119 lesions
High volume	78 (84.8%)
LATITUDE criteria	
Low volume	43 (46.7%)
High volume	49 (53.3%)
Castration-sensitive vs -resistant disease	
Sensitive	61 (66.3%)
Resistant	31 (33.7%)
Previous ADT	
No	49 (53.3%)
Yes	43 (46.7%)
Previous chemotherapy	
No	82 (89.1%)
Docetaxel	10 (10.9%)
Previous new-generation hormonal therapy	
No	81 (88%)
Yes	11 (12%)
Abiraterone	4 (4.3%)
Enzalutamide	7 (7.6%)
Systemic lines before SBRT	
1	31 (33.7%)
2	8 (8.7%)
3	3 (3.3%)
Time from M + to SBRT, median months (range)	2.21 (0.2–76.1)
Total delivered dose, median (range)	42 Gy (18–60)
Number of SBRT fractions	5 (2–8)
SBRT scheme, per lesion	1 (1.1%)
18 Gy/2fr	7 (7.6%)
25 Gy/5fr	16 (17.4%)
32.4 Gy/4fr	1 (1.1%)
32 Gy/4fr	2 (2.2%)
36 Gy/4fr	1 (1.1%)
36 Gy/6fr	8 (8.7%)
40 Gy/4fr	6 (6.5%)
40 Gy/5fr	2 (2.2%)
40 Gy/8fr	1 (1. %)
42 Gy/4fr	5 (5.4%)
45 Gy/6fr	17 (18.5%)
48 Gy/4fr	23 (25.0%)
60 Gy/8fr	2 (2.2%)
BED3, median (range)	157.5 Gy (66.6–240)

low-intermediate risk NCCN disease (3 years DPFS of 60.2%, 95% CI 33–79.3). Even in this case the difference in terms of DPFS was statistically significant ($p = 0.016$). According to Cox proportional hazards with class 1 as the reference, HR for classes 2 and 3 were 0.51 (95% CI 0.26–0.98, $p = 0.046$) and 0.31 (95% CI 0.13–0.70; $p = 0.005$), respectively.

Regarding only castration-sensitive patients, RPA identified two prognostic classes for OS (Fig. 3). Class 1 was represented by patients with only 1 single metastasis, with 3 years OS of 100%. Class 2 (3 years OS of 88.8%, 95% CI 43.3–98.3) included patients with 2 or more metastases.

In terms of DPFS, RPA divided patients into two classes, according to a cutoff value of DFI of 34 months (Fig. 3). Class 1 included patients with DFI < 34 months with 3 years DPFS rate of 14.8% (95% CI 2.89–35.73) and class 2 included patients with DFI ≥ 34 months with 3 years rate of 56.4% (95% CI 30.58–75.90). When analyzing OS for

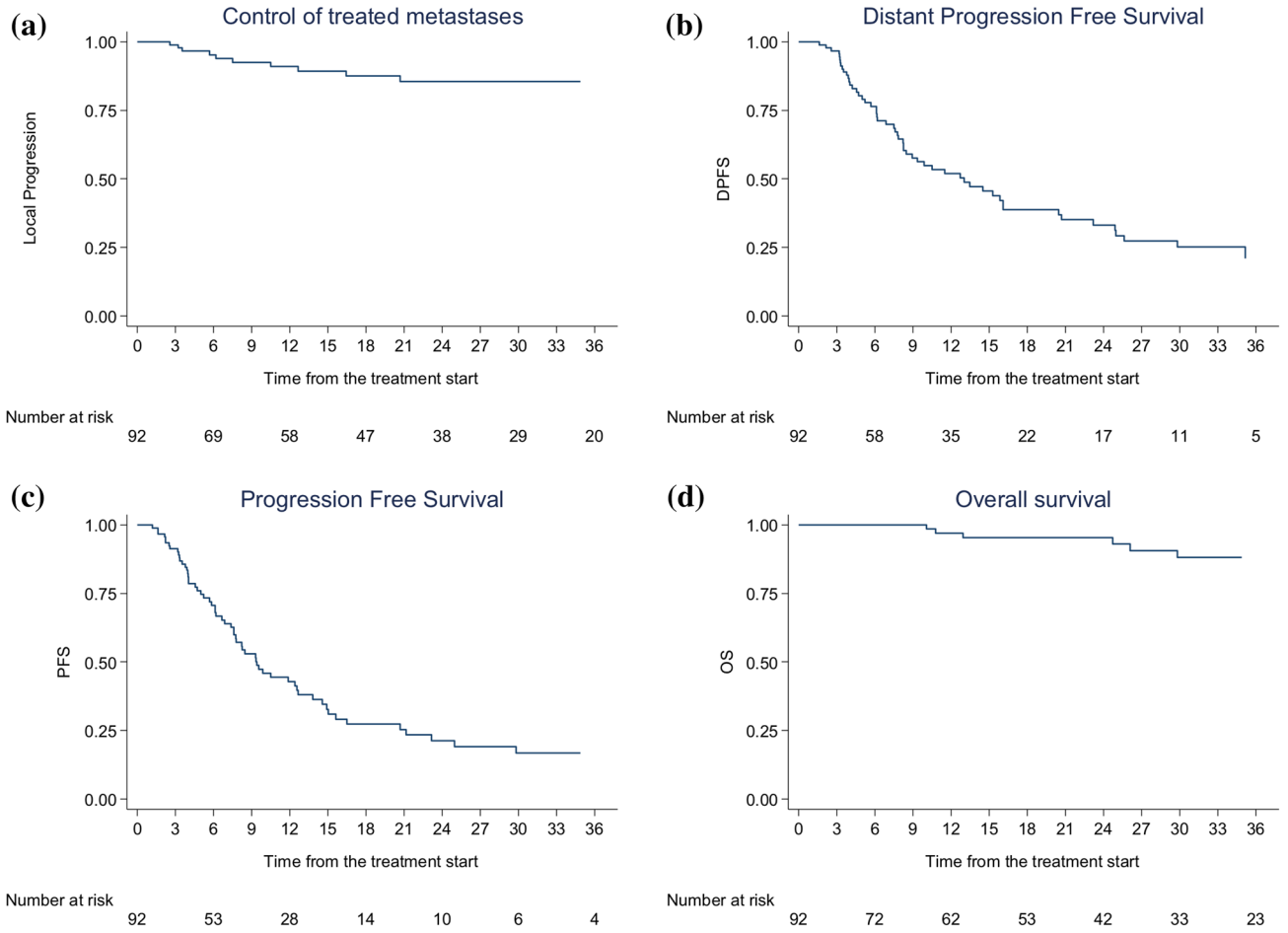

Fig. 1 Kaplan–Meier curves for: **a** control of treated metastases, **b** distant progression-free survival, **c** progression-free survival and **d** overall survival

castration-resistant patients, RPA identified three classes (Fig. 3). Class 1 included patients with low-intermediate risk disease (3 years OS of 88.9%, 95% CI 43.3–98.3) and class 2 included patients with high-risk PC and DFI ≥ 72 months (3 years OS of 83.3%, 95% CI 27.3–97.4). Class 3 included patients with high-risk disease and DFI < 72 months (3 years OS of 72%, 95% CI 34–90.4). For DPFS, 2 classes were detected according to NCCN risk: class 1 for low-intermediate risk (3 years DPFS 22.2%, 95% CI 1.5–58.2) and class 2 for high risk (3 years DPFS 6.3%, 95% CI 0–23.9).

Discussion

In the present study, we evaluated the presence of patient's characteristics and disease's factors predictive for survival outcomes in oligometastatic PC patients treated with SBRT. We observed a median survival of 91.6 months and a PFS of 9.4 months. Despite high rates of LC (only ten patients developed infield progression), the appearance of new metastases during follow-up was diagnosed in 55 patients (50.6%). These results are in line with the data reported by the most recent literature (Triggiani et al. 2019; Franzese et al. 2018; Ingrosso et al. 2017). Ost et al. (2017) conducted a randomized trials comparing surveillance versus MDT in a sample of 62 hormone naïve metastatic PC patients. With a median follow-up of 3 years, the median ADT-free survival was 13 months for surveillance group versus 21 for the treatment group. In terms of PFS, the median time until progression was 6 months for the surveillance group, as compared with 10 months for the MDT group ($p = 0.03$). Another trial (Decaestecker et al. 2014) evaluated the possibility to delay ADT with repeated SBRT. The study included hormone-sensitive patients with 1–3 metastases. Fifty patients with 70 metastatic lesions were included with a median PFS of 19 months (95% CI 13–25). Triggiani et al. (2017) produced a multicentric study oligorecurrent hormone naïve and oligoprogressive castration-resistant PC. A total of 100 oligorecurrent PC and 41 oligo-castration-resistant

Table 2 Univariate and multivariate analyses for overall survival

	Univariate			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, > 65 years	3.56	0.41–30.4	0.245	–	–	–
PS	1.92	0.79–4.67	0.149	–	–	–
Initial PSA	1.01	0.98–1.03	0.301	–	–	–
Gleason score	**3.28**	**1.70–6.35**	**0.000**	3.69	0.94–14.47	0.061
NCCN class risk	**12.93**	**1.67–100.11**	**0.014**	0.10	0.00–12.72	0.353
Time to biochemical relapse, months	1.00	0.99–1.01	0.191	–	–	–
Time to diagnosis of metastases, months	1.00	0.99–1.01	0.343	–	–	–
Time from biochemical relapse to diagnosis of metastases, months	0.977	0.91–1.03	0.462	–	–	–
Number of treated metastases	1.24	0.56–2.73	0.593	–	–	–
PSA pre-radiotherapy	1.01	0.95–1.08	0.598	–	–	–
PSA doubling time	1.03	0.98–1.09	0.158	–	–	–
PSA velocity	1.00	0.99–1.07	0.100	–	–	–
Imaging before radiotherapy, PSMA-PET	7.62	0	1.000	–	–	–
Previous ADT	**10.24**	**1.31–79.52**	**0.026**	**1.16**	**7.55–17.9**	**0.000**
Previous Chemotherapy	**4.69**	**1.16–18.9**	**0.030**	4.43	0.03–561.63	0.547
Sistemic lines before SBRT	**2.21**	**1.16–4.21**	**0.015**	0.22	0.00–17.83	0.501
Castration resistance	**12.88**	**1.66–99.87**	**0.014**	Insufficient events	–	–
CHARTEED criteria	1.07	0.13–8.79	0.946	–	–	–
LATITUDE criteria	**4.95**	**1.32–18.60**	**0.018**	1.92	0.42–8.67	0.396

Bold factor with p value < 0.005

Table 3 Univariate and multivariate analyses for progression-free survival

	Univariate			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, > 65 years	0.69	0.37–1.30	0.258	–	–	–
PS	0.95	0.65–1.38	0.804	–	–	–
Initial PSA	1.00	0.99–1.01	0.432	–	–	–
Gleason Score	0.97	0.81–1.16	0.756	–	–	–
NCCN class risk	0.82	0.51–1.32	0.432	–	–	–
Time to biochemical relapse, months	**0.99**	**0.98–0.99**	**0.043**	0.99	0.98–1.00	0.064
Time to diagnosis of metastases, months	0.99	0.98–1.00	0.066	–	–	–
Time from biochemical relapse to diagnosis of metastases, months	1.00	0.98–1.01	0.881	–	–	–
Number of treated metastases	**1.81**	**1.14–2.89**	**0.012**	1.55	0.88–2.73	0.123
PSA pre-radiotherapy	1.01	0.99–1.04	0.170	–	–	–
PSA doubling time	1.01	0.98–1.04	0.442	–	–	–
PSA velocity	**1.01**	**1.00–1.02**	**0.037**	1.00	0.99–1.02	0.194
Imaging before radiotherapy, PSMA-PET	0.68	0.24–1.91	0.475	–	–	–
Previous ADT	1.55	0.93–2.60	0.091	–	–	–
Previous Chemotherapy	**2.61**	**1.25–5.42**	**0.010**	1.80	0.49–6.67	0.373
Sistemic lines before SBRT	**1.44**	**1.05–1.98**	**0.022**	1.08	0.65–1.78	0.747
Castration resistance	1.35	0.81–2.25	0.247	–	–	–
CHARTEED criteria	0.85	0.44–1.65	0.640	–	–	–
LATITUDE criteria	0.84	0.50–1.40	0.509	–	–	–

Bold factor with p value < 0.005

Table 4 Univariate and multivariate analyses for outfield progression-free survival

	Univariate			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, > 65 years	**0.50**	**0.26–0.95**	**0.037**	0.50	0.21–1.17	0.114
PS	0.91	0.61–1.37	0.680	–	–	–
Initial PSA	1.00	0.99–1.01	0.167			
Gleason score	1.09	0.91–1.31	0.310			
NCCN class risk	1.26	0.78–2.03	0.328	–	–	–
Time to biochemical relapse, months	**0.98**	**0.98–0.99**	**0.004**	0.98	0.96–1.01	0.385
Time to diagnosis of metastases, months	**0.99**	**0.98–0.99**	**0.007**	0.99	0.97–1.01	0.808
Time from biochemical relapse to diagnosis of metastases, months	0.947	0.98–1.01	0.947	–	–	–
Number of treated metastases	1.45	0.89–2.37	0.135	–	–	–
PSA pre-radiotherapy	1.02	0.99–1.04	0.105	–	–	–
PSA doubling time	1.01	0.98–1.04	0.358	–	–	–
PSA velocity	**1.01**	**1.00–1.02**	**0.017**	**1.01**	**1.00–1.02**	**0.049**
Imaging before radiotherapy, PSMA-PET	0.94	0.33–2.64	0.913	–	–	–
Previous ADT	**1.80**	**1.05–3.11**	**0.033**	1.15	0.24–5.53	0.853
Previous Chemotherapy	**2.79**	**1.34–5.77**	**0.006**	1.77	0.35–8.82	0.484
Sistemic lines before SBRT	**1.59**	**1.15–2.19**	**0.005**	1.08	0.43–2.68	0.863
Castration resistance	**1.74**	**1.01–2.97**	**0.043**	1.36	0.28–6.44	0.696
CHARTEED criteria	1.01	0.49–2.08	0.962	–	–	–
LATITUDE criteria	1.03	0.60–1.77	0.908	–	–	–

Bold factor with p value < 0.005

Table 5 Univariate and multivariate analyses for local control

	Univariate			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age, > 65 y	2.35	0.29–18.56	0.417	–	–	–
PS	1.92	0.86–4.21	0.108	–	–	–
Initial PSA	0.96	0.87–1.06	0.472	–	–	–
Gleason Score	0.72	0.46–1.12	0.152	–	–	–
NCCN class risk	0.54	0.19–1.53	0.253	–	–	–
Time to biochemical relapse, months	1.00	0.99–1.02	0.319	–	–	–
Time to diagnosis of metastases, months	1.00	0.99–1.01	0.415	–	–	–
Time from biochemical relapse to diagnosis of metastases, months	0.99	0.95–1.03	0.873	–	–	–
Number of treated metastases	0.51	0.12–2.20	0.517	–	–	–
PSA pre-radiotherapy	1.02	0.96–1.08	0.477	–	–	–
PSA doubling time	1.01	0.96–1.07	0.491	–	–	–
PSA velocity	0.98	0.92–1.05	0.675	–	–	–
Imaging before radiotherapy, PSMA-PET	1.24	0.15–9.99	0.834	–	–	–
Previous ADT	1.00	0.29–3.48	0.988	–	–	–
Previous chemotherapy	5.32	0	1.000	–	–	–
Sistemic lines before SBRT	0.62	0.23–1.65	0.343	–	–	–
Castration resistance	0.84	0.23–2.98	0.788	–	–	–
CHARTEED criteria	0.77	0.16–3.64	0.746	–	–	–
LATITUDE criteria	0.87	0.25–3.02	0.831	–	–	–
Radiotherapy dose, BED3	0.99	0.98–1.00	0.812	–	–	–

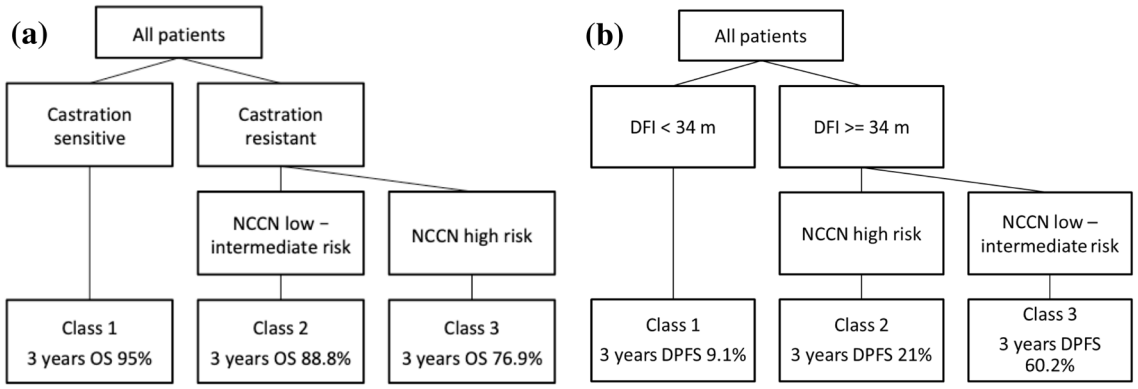

Fig. 2 Recursive partitioning models for: **a** overall survival, **b** distant progression-free survival

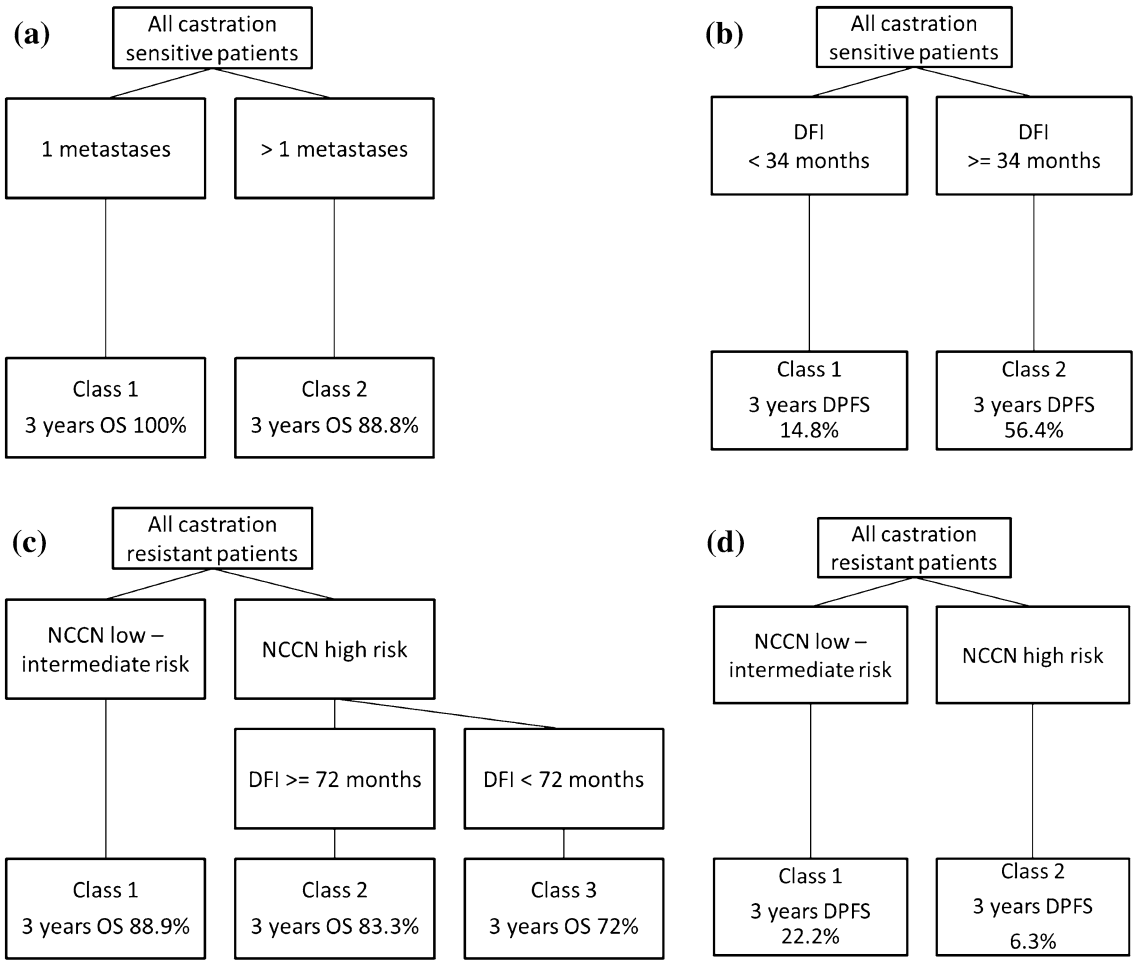

Fig. 3 Recursive partitioning models for: **a** overall survival in castration sensitive, **b** distant progression-free survival in castration sensitive, **c** overall survival in castration resistant, **d** distant progression-free survival in castration resistant

PC were analyzed. Regarding the first group, the median PFS was 17.7 months, with 1 and 3 years rate of 64.4% and 26.6%, respectively. For castration-resistant patients, the 1-year rate of DPFS was 43.2% with a median value of 11 months.

Considering these promising but not yet satisfying results, it seems necessary to better define criteria for selection of oligometastatic patients eligible to MDT, together with the identification of patients who could benefit the most from an association of SBRT with systemic therapy. In our RPA analysis, all identified nodes had OS rates higher than 50%; however, DPFS was significantly reduced from one class to another. While castration resistance seems to be the main factor affecting OS, for DPFS a cutoff value of 34 months of DFI seems to be a more relevant factor. The 3-year DPFS rate of 60% in low-intermediate risk with DFI ≥ 34 months will be reduced to only 9% in patients with DFI < 34 months. DFI remains a significant factor for RPA classes of castration-sensitive patients, while NCCN class risk appeared to be more relevant for castration resistance.

The importance of time between treatment of primary tumor and occurrence of metastatic disease has been demonstrated for other sites but not for PC (Hayakawa et al. 2012; Inoue et al. 2012). Hong et al. (2018) conducted a multi-institutional pooled analysis of oligometastatic patients with different primary tumors, including breast, colorectal and PC. Three years PFS for the whole group was 24% and OS was 56%. A DFI > 75 months was considered a positive predictive factor for OS but only for non-breast, non-kidney and non-PC patients. Yamashita et al. (2016) demonstrated the impact of DFI in a cohort of 96 patients affected by lung metastases treated with SBRT. The most common primary tumors were lung and colorectal cancer. The 3 years OS rates for DFI ≥ 24 months and for DFI < 24 months were 69.2% (95% CI 55.5–82.9%) and 29.8% (95% CI 12.7–46.9%), respectively.

Kinetics of PSA value did not influence nodes in RPA but seemed to be statistically significant for DPFS in both univariate and multivariable analyses. An increasing PSAv was associated with a higher risk of progression (HR 1.01, 95% CI 1.00–1.02; $p = 0.049$).

Values of PSAdt and PSAv were considered suggestive of abnormal PET scan in patients submitted to prostatectomy (Castellucci et al. 2010; Rybalov et al. 2013). In particular, Rybalov et al. showed significant difference in area under the curve (AUC) of PSAv 0.730 ($p < 0.001$) to detect a recurrence with the ROC analysis.

A role in the prediction of outcome for PSAv was demonstrated for patients with detectable PSA after radical prostatectomy. Ploussard et al. (2013) observed that the two most powerful predictors were postoperative PSA > 1 ng/ml (OR 3.46, $p = 0.032$) and PSAv > 0.2 ng/ml/year (HR 6.01, $p = 0.001$). The 5-year PFS rate was 81.0% in patients with stable or negative PSAv, compared with 58.4% in those with positive PSAv ($p < 0.001$).

In the setting of oligometastatic disease, PSAv has not been widely investigated in oligometastatic PC. More data have been published regarding the correlation between PSAdt and outcomes (Ost et al. 2017; Decaestecker et al. 2014; Schick et al. 2013).

According to Decaestecker et al. (2014), the value of PSAdt prior to SBRT was a significant predictor for PFS (HR 0.90, 95% CI 0.82–0.99). The median PFS was 12 months for patients with a PSAdt ≤ 3 months compared to 21 months for patients with a longer PSAdt ($p = 0.016$). On the contrary, Ost et al. (2017) did not observe a significant correlation between the effect of MDT and PSAdt or the site of metastases (nodal vs non-nodal) with p values of 0.35 and 0.31, respectively.

We acknowledge the limitations of the present study, including the retrospective nature of the analysis, the limited number of patients and the short follow-up time.

Conclusions

Oligometastatic PC represents nowadays a setting of interest in which local ablative therapies may play a decisive role for survival and quality of life. Ongoing studies (e.g. NCT03784755, NCT03569241 and NCT03796767) are recruiting patients to recognize the improvement in terms of disease control and survival after MDT treatments including SBRT. In the present study, we recognized the importance of DFI, together with NCCN class risk, as a predictor of new metastases after SBRT. Moreover, also PSA kinetic should be evaluated before an MDT.

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Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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