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Prognostic risk classification for biochemical relapse-free survival in oligometastatic Pet-Choline recurrent prostate cancer.

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Abstract

Introduction: CholinePET/CT is one of the new imaging techniques for the detection of oligometastatic (OM) prostate cancer. The aim of this study was to evaluate the outcomes after initial OM, treatment particularly Metastasis Directed Therapy (MDT), and determine risk groups.

Material and Methods: Multicentric, retrospective study which included patients with hormone-sensitive biological relapse after local treatment with curative intent, and with ≤ 5 CholinePET/CT metastasis. Primary endpoint was biochemical Relapse-Free Survival (bRFS). Risk groups were based on PSA ≥ 0.8 ng/ml and metastatic sites at OM diagnosis.

Results: Between October 2012 and December 2016, 177 patients were included with a median follow-up of 49.02 months. The median bRFS was 39.74 months. In multivariate analysis bone metastases and PSA ≥ 0.8 ng/ml were associated to a worse bRFS. Four risk groups (I to IV HR 5.92 [95%CI, 1.32-26.61]) were observed with a median bRFS not reach for the group I (PSA < 0.8, and nodes met (M1a)), 40.00 months for group II (PSA ≥ 0.8 and M1a), 29.97 months for group III (bone met (M1b) whatever the PSA level) and 22.70 months for group IV (PSA > 0.8 and visceral met (M1c)). MDT plus Androgen Deprivation Therapy (ADT) improved bRFS over MDT alone 48.36 vs 34.16 months (HR 2.12 [95%CI 1.38,3.26]) particularly for group II (HR95%CI 2.09 [1.09,4.00]) and limit of significance for group III (HR95%CI 3.79 [0.88,16.38])..

Conclusions: Prognostic group classification were confirmed: PSA < 0.8 and M1a have a better outcome than patients with M1c and PSA ≥ 0.8 . These results could facilitate patient's selection for prospective clinical trial in OM prostate cancer.

Keywords: Prostate Cancer (PC); Oligometastatic (OM); Choline PET/CT; Metastasis-Directed Therapy (MDT); Androgen Deprivation Therapy (ADT).

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Introduction

Prostate Cancer (PC) is the most common cancer in men, with either localized or locally advanced at diagnosis in 90% of cases ¹.

Approximately 30% of patients radically treated for high or very high risk of PCa have biochemical relapse². Metastatic disease was found in 10-14% of cases by standard imaging by CT and bone scan ^{3 4}.

¹⁸F-Choline PET/CT was the only radiotracer readily available in France for the identification of undetected metastases by conventional imaging, with a combined sensitivity and specificity of 85% [95%CI, 79-89%] and 88% [95%CI, 73-95%] respectively⁵.

Analysis of recurrence after initial local treatment of PC suggests that most patients presented limited numbers and locations of metastatic sites, defining an Oligometastatic (OM) disease⁶.

Metastasis-Directed Therapy (MDT) by mini-invasive surgery or Stereotactic Body Radiation Therapy (SBRT), accurate delivery of a high dose to a specific target has proven its interest in PC and other tumors⁷. MDT could have multiple beneficial effects: limiting metastatic spread, delaying introduction of Androgen Deprivation Therapy (ADT), and Castration Resistance PC (CRPC), avoiding ADT adverse effects while improving quality of life and survival. Confirming these hypotheses could therefore shift the paradigm of a metastatic disease from a palliative situation to a potentially curable disease in a subgroup of selected patients.

Currently, there is no standard-of-care for treating hormone-sensitive OM PC recurrence. Prognostic factors have recently been identified for OM detected by PSMA PET treated by MDT, with determination of prognostic risk classification for biochemical relapse⁸.

This study highlights the results of a multi-institutional, retrospective analysis regarding the different therapeutic managements for hormone-sensitive OM in first relapse after definitive local treatment, diagnosed by Choline PET/CT, and identification of prognostic group classification for biochemical relapse in this population.

Methodology

Study design

After local review board approval, we performed a retrospective, multi-institutional analysis of different therapeutic strategies for metastatic hormone-sensitive PC patients on Choline PET/CT after an initial local treatment with curative intent.

Patients with a biochemical recurrence, with up to five hypermetabolic target lesions on Choline PET/CT with at least one extra-prostatic (bed) were included. Each lesion was counted separately and contributed to the total number of OM lesions. A minimum delay of 12 months was applied between the end of ADT effect and Choline PET/CT.

MDT corresponds to mini-invasive surgery or EBRT (External Beam Radiotherapy), alone or combined with ADT. Patients treated by ADT alone were recorded. The multidisciplinary uro-oncology team approved all cases.

Post-Treatment follow-up, physical examination and PSA dosage, was orchestrated every 3 to 6 months. Imaging was repeated if warranted by symptoms or rising PSA using Choline PET/CT if PSA level was <10 ng/mL, otherwise by CT scan and bone scan.

Statistical Analysis

The statistical analysis was carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA). Survival estimates were calculated with the Kaplan-Meier method and compared with log-rank test. The association of categorical factors with survival was assessed using univariate and multivariate Cox models and was tested using Log-rank and Wald tests. Statistical significance was set at P value <0.05.

The primary endpoint was biochemical Recurrence-Free Survival (bRFS), defined as the time between the diagnosis of OM disease to PSA progression (or radiologic progression or death depending on which progression occurred earlier). ADT FS was defined as the time of OM diagnosis to the time of palliative ADT for new metastasis or tumor progression. Univariate and multivariate Cox regression analyses were assessed for risk factors for biochemical relapse. Factors were selected from the results of the Vogel *et al.* study taking account our different populations with initial definitive local treatment by prostatectomy and or radiotherapy⁸. The selected factors were: initial clinical stage \leq T2c vs \geq T3a, N0 vs N1, Gleason score \leq 7a vs \geq 7b, age at relapse, PSA <0.8 or \geq 0.8 ng/ml and the most important

location of metastasis: pelvic nodes only vs M1a extra pelvic nodes vs M1b bone metastasis vs M1c visceral. Multiple cox regression analysis was based on Vogel's and our study's significant factors. As the possible cofounder of additive ADT was already analyzed, administration cox regression's calculation was unadjusted for additive ADT

By applying Vogel's decision tree to our data, four groups of patients were created: low, intermediate, high and very high risk.

Results

Patient characteristics

Between October 2012 and December 2016, 177 patients were enrolled in this retrospective study. Patient's characteristics at the time of local prostate disease and OM disease were recorded in Table 1. Clinical stage was equal to or less than T2c for 81.68% of them. Prostatectomy or combined with salvage radiotherapy was the primary treatment for 74.01% of patients. Median delay between PC diagnoses to the first OM recurrence was 66.82 [range, 2.26-233.20] months (Table 2). The median PSA at the time of OM diagnosis was 2.67 ng/ml [range, 0.14-68.90]. A majority of patients had PSA \geq 0.8 (85.63%). The number of metastatic sites by Choline PET/CT was 405 for the 177 patients with a median of 2 lesions [1.00-5.00] per patient. The most frequent sites were lymph nodes (72.32%), followed by bone metastases (24.29 %). Only six patients (3.39%) had visceral metastasis. Median delay between the end of ADT for localized PC and OM was 26.85 months [range, 0.49 ; 137.71] only 3 patients had relapse less than 194 days from the end of ADT .

For 61.02% (n=108) patients the treatment for OM disease was MDT, by EBRT for 92.59% (n=100), combined with ADT for 66.67% (n=72).

For patients with nodes only relapse, 13% received SBRT only to involved nodes on Choline PET/CT and 87% an extended prophylactic radiotherapy with a boost to the involved nodes. For patients treated for bone or visceral metastases SBRT was used for a total dose of 30 or 35 Gy with 5 fractions.

The median duration of concomitant ADT with MDT was 6.0 months [range, 2.89-41.90]. The others patients had surgery (7.41%), 2 of them with.

68 patients (38.41%) received ADT alone at the time of OM later with MDT the for second OM recurrence for 11 of them (16.18%). The median long term ADT-FS was 53.25 months (4.44 years) [95%CI, 43.93-;74.89].

Oncological outcomes

The median follow-up was 49.02 months [95%CI, 44.29;53.44] from the time of OM diagnosis. The median bRFS was 39.74 months [95%CI, 34.39;43.67].

In univariate analyses (Table 3), the factors associated with bRFS were the clinical tumoral ($\leq T2c$ vs $\geq T3a$ HR 0.62 [95%CI, 0.35;1.08]) and node stages (N0 vs N1 HR 0.26 [95%CI, 0.06;1.07]) at initial diagnosis of localized PC. The PSA < 0.8 ng/ml was identified as a significant prognostic factor for better bRFS at OM diagnosis < 0.8 vs ≥ 0.8 (HR 0.33 [95%CI, 0.13;0.81]). Pelvic nodes were a prognostic factor for better bRFS (HR 1.84 [95%CI, 1.24;2.73]). The presence of bone metastases was a prognostic factor for a lesser bRFS (MHR 0.51 [95%CI, 0.33;0.79]). Patients having received only MDT were significantly associated with a more deleterious bRFS ($p < .001$ HR 2.12 [95%CI, 1.38;3.26]).

In multivariate analysis (Table 4) not adjusted on ADT with MDT, M1a and PSA > 0.8 were associated with a significant improvement in bRFS. After adjustment on ADT which was highly significant ($p=0.004$ HR 1.93 [95%CI, 1.24;3.00]), there was only a trend towards significance for the presence of bone metastases ($p=0.086$ HR 0.67 [95%CI, 0.43;1.06]).

Factors present in Vogel's decision tree were used to create 4 risk groups (Figure 1): group I low risk (PSA < 0.8 and M1a), group II (PSA ≥ 0.8 and M1a, median 40.00 months)(HR 4.49 [95%CI, 1.40;14.33] p Wald= 0.011), group III M1b whatever the PSA, median 29.97 months (HR 7.11 [95%CI, 2.16;23.39] p Wald=0.001), group IV (PSA ≥ 0.8 , M1c median 22.70 months (HR 5.92 [95%CI, 1.32;26.61] p Wald= 0.020) (figure 1).

MDT associated to ADT improved bRFS over MDT alone (medians 48.36 vs 34.16 months HR 2.12 [95%CI, 1.38;3.26] $p < .001$). The risk groups were analyzed by treatment strategies: MDT vs MDT + ADT and the median bRFS were for group I: 41.90 months vs NR, for group II: 23.21 months vs 41.93 months, for group III: 15.77 vs 33.97 months, not reported for group IV with too few patients (Figure 2).

The median bRFS for patients with long-term ADT alone was 34.33 months [95%CI, 26.03;43.67] versus 41.90 months [95%CI, 36.75;48.36] for patients treated by MDT with or without ADT. The PSA declined after MDT alone was observed in 15 out of 35 (42.86%) patients. The number of OM site 1 vs ≥ 2 was not significantly different for bRFS (HR 0.89 [95%CI, 0.59;1.34] $p=0.574$).

The median delay to CRPC was 80.39 months [95%CI, 66.85;NA]. The median metastatic relapse-free survival was 60.79 months [95%CI, 45.38;80.89] and MDT combined with ADT, 74.46 months [95%CI, 42.89;NA], versus ADT alone, 60.79 months [95%CI, 43.77;NA]. The 3- and 5-year overall survival (OS) and disease specific survival (DSS) were 0.96 [95%CI,

0.91;0.98], 0.87 [95%CI, 0.77;0.93], 0.99 [95%CI, 0.96;0.99], and 0.97 [95%CI, 0.93;0.99] respectively.

Discussion

The new metabolic imaging for detecting recurrent PC establishes new metastatic profiles of patients. We reported a retrospective multicentric analysis to assess, with long follow-up (49.02 months [95%CI, 44.29; 53.44]) the management of 177 patients in biochemical relapse after definitive local treatment for PC with OM, defined by 5 or less metastases out of the prostate (bed), diagnosed by CholinePET/CT. Patients were predominantly treated by MDT (61.02%) alone or combined with ADT. In order to determine the population of PC with OM most likely to benefit from MDT we generated risk groups according to PSA and metastatic site involvement as published by Vogel *et al.* for a population of OM recurrence PSMA/PET positive patients treated by MDT⁸.

In our study the median PSA was 2.67 ng/ml [range, 0.14-68.9] it was not a prognostic significance for bRFS as was PSA < 0.8 ng/ml which was significant in multivariate analyses. The cut off value of 0.8 ng/ml was determined in a receiver operating characteristic for patients with oligorecurrent disease detected with [68Ga] PSMA-PET imaging⁸. With recent imaging, new characteristics of oligometastatic disease as emerge, with lower burden tumor than with conventional imaging.

The systemic standard-of-care for hormone-sensitive metastatic PC is based on ADT alone or combined with docetaxel or new generation hormonal therapies^{9 10 11 12 13}. The OM hypothesis suggests a spectrum of metastatic virulence where some metastases are limited and curable with focal therapies. Part of the goal for MDT is to delay the initiation of continuous ADT and other systemic treatment and consequently delays castration resistance and adverse outcomes. Advances in radiotherapy by stereotaxic approach and surgery technics have improved the MDT modalities.

The STOMP trial for hormone-sensitive oligorecurrent (≤ 3 metastases detected by Choline PET/CT scan), randomized MDT (by SBRT or surgery) versus observation (62 patients) and detected an improvement in median ADT-FS from 13 to 21 months (HR, 0.60; 80% CI, 0.40–0.90; $p = .11$)¹⁴.

A phase II trial, included 16% PC, and randomized patients with oligorecurrent disease (≤ 5 metastases), to SBRT to all sites plus standard-of-care or standard-of-care alone¹⁵. The addition of SBRT improved the median overall survival: 28 months (95% CI 19–33) in the control group versus 41.00 months (26–NR) in the SBRT group (HR 0.57, 95% CI 0.30–1.10; $p=0.090$).

The other prospective phase II trial: ORIOLE included 54 recurrent hormone-sensitive PC and ≤ 3 metastases detectable by conventional imaging randomized between SBRT vs observation. Treatment with SABR improved median progression-free survival (NR vs 5.8 months; HR, 0.30; 95%CI, 0.11-0.81; P = .002)¹⁶.

In our cohort the median to long term ADT FS was 53.25 months (4.44 years) [95%CI, 443.93;74.89]. Overall 40.68% of patients received MDT combined with ADT with a median of 6.0 months [95%CI, 2.89-41.90] ADT duration.

The current role of ADT combined with MDT is unknown. The RTOG 9601 and GETUG-AFU 16 two large randomized trials of salvage radiotherapy post prostatectomy (evaluated with standard imaging), have shown improvement with the addition of ADT to salvage radiotherapy over radiotherapy alone^{17 18}.

A retrospective multi-centre study of 305 patients with biochemical relapse and PSMA PET–positive oligorecurrence compared MDT +ADT versus MDT alone and observed a significant improved bRFS with the ADT combination and remained an independent factor (hazard ratio 0.28, 95% confidence interval 0.16–0.51; p < 0.0001) but was not significantly different for patients with ADT lasting less than 6 months over MDT alone (p = 0.121)¹⁹.

The combination of ADT to MDT improved bRFS over MDT alone for risk group II and III of our population (group II: median 23.21 vs 41.93 months (p=0.023 HR 2.09 [95%CI, 1.09;4.00]), for group III: median 15.77 vs 33.97 months (p=0.057, HR 3.79 [95%CI, 0.88;16.38]) for MDT alone vs MDT +ADT respectively). The difference was not significant for group I. Is MDT alone the better treatment for this specific low risk group? Prognostic factors that help to select OM PC most likely to benefit from MDT can be generated, thereby empowering clinicians and patients to make well-informed treatment decisions.

In a retrospective analysis the John HOPKINS isolated factors which appear to be associated with prolonged time to failure on multivariable analysis following MDT include castration-sensitive disease, the use of ADT, and smaller tumor volumes²⁰.

An internally validated risk classification for bRFS after PSMA-PET-guided MDT was developed in a retrospective analysis on 292 patients⁸. PSA at recurrence ≥ 0.8 ng/mL, metastatic sites location, were significantly associated with biochemical relapse. In our retrospective analysis the same level of PSA and metastatic sites were significant and 4 risk groups have been defined with a median bRFS not reached for the first group, to 22.70 months for the fourth one (HR 5.92 [95%CI, 1.32;26.61]) with a p value of 0.002, with a median follow up of 49.02 months (Figure 1).

The PSA level was a significant cut off for bRFS. In our population detected with PET Choline less sensitive than PSMA PET, only 25 patients (14.13%) were less than 0.8 ng/ml.

The PSA level was a significant factor for bRFS in local salvage radiotherapy, but the information is lacking for OM disease. If high volume disease (defined by visceral metastases and or 4 or more bone metastatic sites with one out the axis, evaluated with standard imaging) is a prognostic factor for survival, for mHSPC treated with ADT alone or combined with docetaxel or next generation hormonal agents, it is not well defined in OM situation ²¹. No data is currently available to determine the prognosis of tumor burden with new imaging for patients with OM disease. Are the location and the PSA level at the diagnosis of oligo recurrent disease could help to select patients who could benefit of MDT?

The OM paradigm has revolutionized our understanding of the metastatic state, with transformative treatment implications²². Emerging evidence supports the use of a locally ablative method to alter the metastatic disease trajectory, with significant improvements in patient outcomes demonstrated in randomized trials. More careful patient selection is essential to ensure that MDT alone or combined is offered to those most likely to benefit. Several prospective phases III are ongoing to better define which patients benefit from MDT alone or combined with systemic therapy, as well as the magnitude of this benefit, and ultimately further establish this as a new paradigm of management for patients with oligometastatic and oligoprogressive cancer.

Strengths and limitations.

This work is distinguished by the number of patients included, the multi-institutional enrollment, with a multidisciplinary approach, and the long median follow-up.

Limitations are the study's retrospective nature and the heterogeneity of studied population. This concerns the initial therapeutic modalities, clinical presentations of OM recurrence, therapeutic strategies available for OM recurrence treatment. The metastatic lesions were histologically confirmed in only 4% of patients.

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Tables and graphics

Table 1.
Patients characteristics at diagnosis of localized prostate cancer (n=177)

Age at diagnosis (years), median [range]		63.00 [46.60-84.84]
PSA at initial diagnosis (ng/ml), median [range]		10.00 [0.15-130.00]
Gleason score biopsy, n (%)		
	≤ 7a (≤ ISUP II)	81 (47.09)
	≥ 7b (≥ ISUP III)	91 (52.91)
Initial T stage, n (%)		
	≤ T2c	107 (81.68)
	≥ T3a	24 (18.32)
Initial N stage, n (%)		
	N0	124 (89.21)
	N1	2 (1.44)
	Nx	13 (9.35)
Primary therapy, n (%)		
	EBRT +/- ADT	40 (22.60)
	Prostatectomy	68 (38.42)
	Prostatectomy + salvage EBRT	63 (35.59)
	Brachytherapy or HIFU ± ADT	6 (3.39)

Table 2.
Patients characteristics at the time of oligometastatic diagnosis (n=177)

Age (years), median [range]		68.97 [47.21-88.47]
Diagnosis-OM (months), median [range]		66.82 [2.26-233.20]
PSA ng/ml, median [range]		2.67 [0.14;68.9]
	PSA \geq 0.8, n (%)	149 (85.63)
	PSA < 0.8, n (%)	25 (14.37)
PSA doubling time, median [range]		4.80 [0.60-158.0]
Number of choline-positive lesions, Median [range]		2.00 [1.00-5.00]
	1, n (%)	68 (38.42)
	2, n (%)	45 (25.42)
	3, n (%)	27 (15.25)
	4, n (%)	19 (10.74)
	5, n (%)	18 (10.17)
Most important metastatic site, n (%)		
	Pelvic nodes	95 (53.67)
	M1a Extra pelvis lymph nodes	33 (18.64)
	M1b Bone metastasis	43 (24.29)
	M1c visceral	6 (3.39)
Treatment of first OM recurrence, n (%)		
	EBRT + ADT	72 (40.68)
	EBRT	28 (15.82)
	Surgery	6 (3.39)
	Surgery + ADT	2 (1.13)
	ADT alone	57 (32.20)

	ADT alone but MDT for later OM recurrence	11 (6.21)
	No treatment (patient refusal)	1 (0.57)
ADT combined with MDT, n (%)		74 (41.81)
Concomitant ADT with MDT (months), Median [range]		6.00 [2.89-41.90]

ADT : androgen deprivation therapy, EBRT: external beam radiotherapy, MDT: metastases directed therapy, OM: oligometastatic

Table 3.
Univariate cox regression of prognostic factors for biological relapse

Criteria	Contrast	P-value	Hazard Ratio [CI 95%]
Initial T stage	≤T2c vs ≥T3a	0.088	0.62 [0.35,1.08]
Initial N stage	N0 vs N1	0.044	0.26 [0.06,1.07]
Initial Biopsy Gleason score	≤7a vs ≥7b	0.876	0.97 [0.65,1.45]
PSA (ng/mL) at OM	< 0.8 vs ≥ 0.8	0.011	0.33 [0.13,0.81]
PSA (ng/mL) at OM	< 2.67 vs ≥ 2.67	0.069	0.69 [0.46,1.03]
Age at relapse	>60 yr vs ≤60 yr	0.221	0.71 [0.41,1.23]
Pelvic lymph node	no vs yes	0.002	1.84 [1.24,2.73]
M1a extra pelvic Lymph node	no vs yes	0.547	0.86 [0.54,1.39]
M1b bone metastasis	no vs yes	0.002	0.51 [0.33,0.79]
M1c visceral metastasis	no vs yes	0.584	0.76 [0.28,2.06]
Nbr of metastases	>1 vs 1	0.574	0.89 [0.59,1.34]
ADT combined with MDT	no vs yes	<.001	2.12 [1.38,3.26]

Table 4.
Multivariate analysis

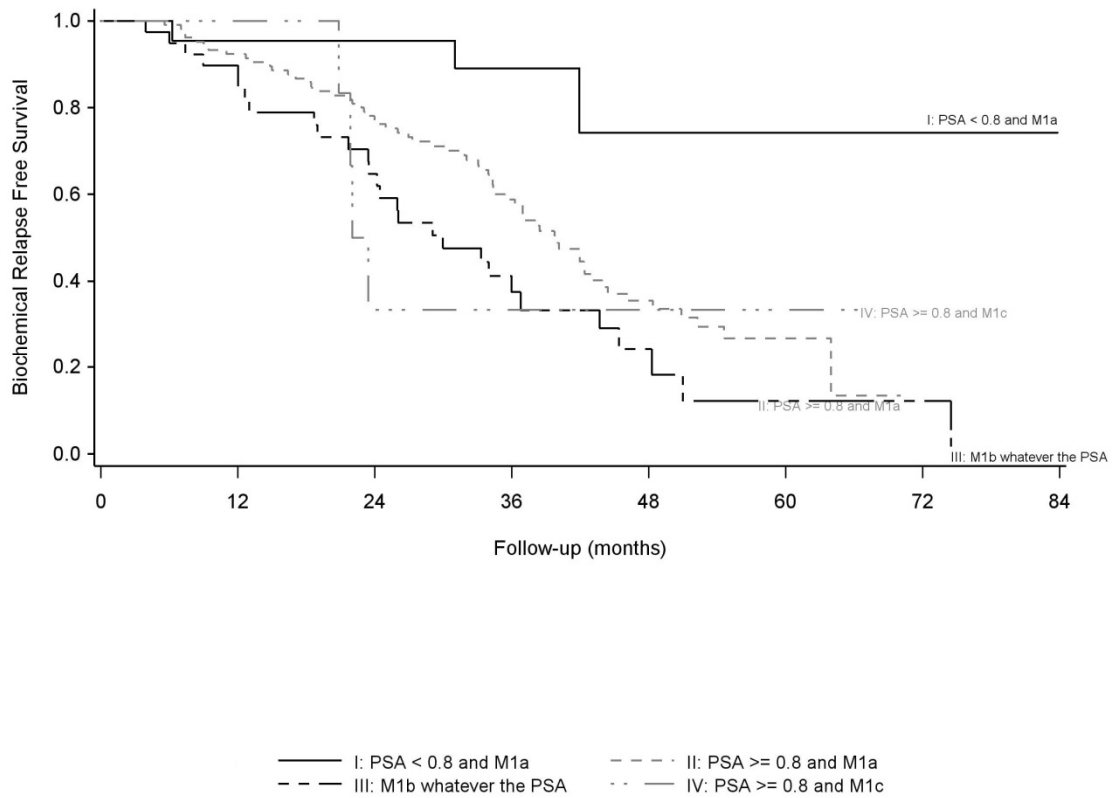
Multivariate analysis for bRFS without adjustment on ADT

Criteria	Contrast	P-value	Hazard Ratio [CI 95%]
M1b bone metastasis	no vs yes	0.032	0.61 [0.39,0.96]
M1c visceral metastasis	no vs yes	0.556	0.74 [0.27,2.04]
PSA (ng/mL) at OM	< 0.8 vs ≥0.8	0.065	0.45 [0.19,1.05]

Multivariate analysis for bRFS with adjustment on ADT

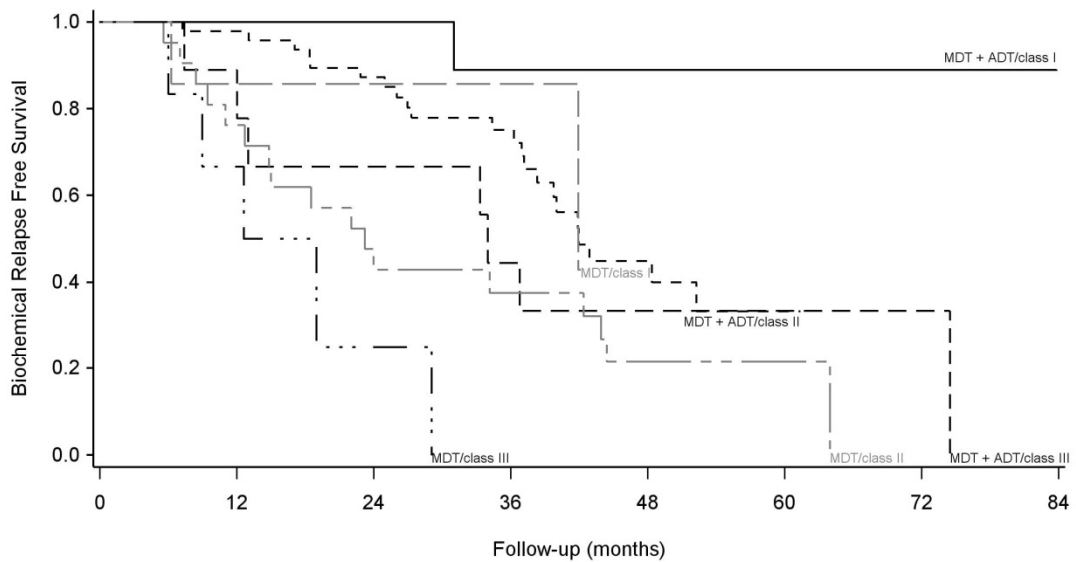
Criteria	Contrast	P-value	Hazard Ratio [CI 95%]
ADT combined with MDT	no vs yes	0.004	1.93 [1.24,3.00]
M1b bone metastasis	no vs yes	0.086	0.67 [0.43,1.06]
M1c visceral metastasis	no vs yes	0.762	0.85 [0.31,2.37]
PSA (ng/mL) at OM	< 0.8 vs ≥ 0.8	0.112	0.50 [0.22,1.17]

Figure 1.
Kaplan-Meier for biochemical relapse-free survival, for risk groups (I-IV).



Group (n)	Median (months) [95%CI]	HR [95%CI]	Wald p-value
I: PSA < 0.8 and M1a (22)	NR	1	
II: PSA ≥ 0.8 and M1a (105)	40.00 [34.39,43.90]	4.49 [1.40,14.33]	0.011
III : M1b whatever the PSA (41)	29.97[23.41,36.75]	7.11 [2.16,23.39]	0.001
IV: PSA ≥ 0.8 and M1c (6)	22.70[20.85,,]	5.92 [1.32,26.61]	0.020

Figure 2.
Kaplan-Meier for biochemical relapse-free survival, for risk groups (I-III)
according treatment MDT or MDT + ADT.



— MDT + ADT/class I - - - MDT + ADT/class II - - - MDT + ADT/class III
 - - - MDT/class I - · - MDT/class II · · - MDT/class III

Group (n)	Treatment	Median (months) [95%CI]	HR 95%CI	p-value
I (14)	MDT +ADT	non estimable	1	
I (7)	MDT	41.90[6.26,.]	3.52 [0.32,38.93]	0.274
II (47)	MDT +ADT	41.93[37.15,.]	1	
II (21)	MDT	23.21[12.69,43.90]	2.09 [1.09,4.00]	0.023
III (9)	MDT +ADT	33.97[7.38,74.46]	1	
III (6)	MDT	15.77[6.00,29.05]	3.79 [0.88,16.38]	0.057

ADT : androgen deprivation therapy, MDT: metastases directed therapy