

Scientific Article

Clinical Outcomes of Combined Prostate- and Metastasis-Directed Radiation Therapy for the Treatment of De Novo Oligometastatic Prostate Cancer



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Abstract

Purpose: The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial reported overall survival benefits for prostate-directed radiation therapy (PDRT) in low-burden metastatic prostate cancer. Oligometastasis-directed radiation therapy (ORT) improves androgen deprivation therapy (ADT)-free and progression-free survivals. Comprehensive PDRT + ORT to all detectable metastases may offer benefit for de novo oligometastatic prostate cancer (DNOPC) and is under prospective study; given few available benchmarks, we reviewed our institutional experience.

Methods and Materials: Forty-seven patients with DNOPC with predominantly M1b disease received neoadjuvant, concurrent, and adjuvant ADT plus PDRT + ORT to 1 to 6 oligometastases. Gross pelvic (N1) nodes were not considered oligometastases unless focally targeted without broader nodal coverage. Outcomes were analyzed from radiation therapy (RT) start using Kaplan-Meier, competing risks, and Cox regression. Median follow-up was 27 (95% confidence interval, 16-42) months.

Results: At 1- and 2-years post-RT, cumulative incidence of distant metastatic progression (DMP) was 21% and 32%, whereas overall survival was 90% and 87%, respectively. Neuroendocrine/intraductal histology, prostate-specific antigen (PSA) < 20, and detectable PSA after PDRT + ORT were associated with increased DMP risk; number and location of oligometastases were not. Local failure was rare, with 3 prostate recurrences and progression of 10 treated oligometastases during follow-up. After neoadjuvant ADT, 9 (19%) patients had undetectable PSA (<0.05 ng/mL), which increased to 32 (68%) after PDRT + ORT. Overall 2-year incidence of biochemical recurrence (BCR) and development of castrate resistance were 23% and 36%, respectively. Undetectable PSA post-RT was associated with lower risk of BCR (hazard ratio, 0.19; $P = .004$) and DMP (hazard ratio, 0.26; $P = .025$). Overall, 23 (49%)

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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patients were trialed off ADT; 16 (70%) had testosterone recovery (>150 ng/dL) and, of these, 5 had subsequent PSA rise and restarted ADT 2 to 21 months postrecovery. The remaining 11 were maintained off ADT without BCR. Median noncastrate duration was 8 months; 7 patients had normalized testosterone for >1 year.

Conclusions: A comprehensive, radiotherapeutic-based treatment strategy has favorable clinical outcomes and can produce prolonged noncastrate remissions in a subset with DNOPC.

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Introduction

De novo metastatic castrate-sensitive prostate cancer (mCSPC) is rare, reflecting less than 5% of new diagnoses; however, its incidence is rising.^{1,2} Those with de novo mCSPC may have more aggressive disease and poorer respective outcomes compared to men who develop distant metastases later in the disease course.³ However, contemporary understanding is evolving and despite common classification, mCSPC is likely very heterogeneous, with variable courses ranging from indolent to very aggressive.^{4,5}

The standard of care for mCSPC remains androgen deprivation therapy (ADT) with consideration of novel antiandrogens or chemotherapies.^{6,7} However, across oncology, and particularly for prostate cancer (PC), there is growing acceptance that oligometastatic disease might carry a more favorable prognosis.⁸⁻¹⁰ Thus, contemporary treatment of newly diagnosed oligometastatic cancers has evolved away from palliation to inclusion of metastasis-directed therapies (MDTs).

Translating this paradigm to de novo oligometastatic PC (DNOPC) necessitates local therapy to the primary prostate tumor and limited distant sites. Several retrospective and database studies suggest that treating metastatic PC (mPC) with ADT plus prostate-directed radiation therapy (PDRT) has improved overall survival (OS) versus ADT alone.¹¹⁻¹⁵ Prospectively, a similar effect was demonstrated posthoc in the HORRAD trial, where men with low volume metastatic disease (defined as <5 metastases) who received PDRT + ADT had improved OS versus ADT alone.¹⁶ Although suggestive, this effect did not achieve statistical significance; however, this study may have been underpowered.¹⁷ Subsequently, the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial confirmed this effect, where OS was significantly improved in patients with low metastatic burden (defined as <4 total bone metastases or any number of exclusively vertebral/pelvic osseous sites) treated with PDRT versus standard of care¹⁸; the Systemic Treatment Options for Cancer of the Prostate (STOPCAP) meta-analysis of the HORRAD and STAMPEDE trials reported similar results.¹⁹

Excellent local control of PC metastases after stereotactic body radiation therapy (SBRT) has motivated

several prospective trials of SBRT for oligorecurrence. The Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) trial found that MDT to ≤ 3 metastases improved ADT-free survival versus surveillance.²⁰ The Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) study was similarly designed, and found SBRT reduced progression of new metastases.²¹ The multihistology Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Disease (SABR-COMET) study (16% PC) was the first prospective demonstration that SBRT improves OS over standard palliative radiation therapy (RT) for oligorecurrence with controlled primary tumors.²²

Building on the results from these studies, we hypothesized that a comprehensive approach with ADT plus local prostate- and metastasis-directed therapies could offer a survival benefit in DNOPC. Pilot data from 20 patients with DNOPC treated at our institution demonstrated that multimodal treatment with ADT plus prostatectomy/lymphadenectomy and SBRT to limited metastases could produce durable noncastrate remissions.²³ Although promising, this approach is limited, as many patients with DNOPC are not surgical candidates, and a strategy of PDRT + RT to appreciable oligometastases may be preferable. To our knowledge, there are scarce data regarding comprehensive, definitive RT in DNOPC, and we reviewed our institutional experience.

Methods and Materials

Study design

After institutional review board approval, we performed a retrospective cohort study of patients with DNOPC treated at our institution who received ADT with PDRT plus preplanned RT to all radiographically appreciable oligometastases (PDRT + ORT). Given the heterogeneity of the oligometastatic definition and to maximize hypothesis generation, there was no a priori upper limit for the number of baseline-treated oligometastases. Patients were treated at a specialized comprehensive cancer center from November 2007 to March 2018.

Diagnosis of oligometastatic lesions

Diagnostic modalities were nonstandardized and determined at the discretion of the treating physicians. Several imaging modality studies were used for initial diagnosis, including pelvic or whole-body magnetic resonance imaging, computed tomography, bone scintigraphy or positron emission tomography (PET) using sodium fluoride, fluorodeoxyglucose or prostate-specific membrane antigen (PSMA) imaging tracers.

Given the potential implications on PDRT field design/dosing and toxicity, we considered 2 bone metastasis classifications: neighboring and non-neighboring. Neighboring osseous metastases were defined as the bony pelvis, acetabulae, proximal femora, and sacrococcyx; all other osseous sites were considered non-neighboring. Patients were typically diagnosed with N1 disease by magnetic resonance imaging, and an involved pelvic lymph node was only considered an oligometastasis for this analysis if the patient received node-directed RT without broader pelvic field RT.

Hormonal and systemic therapy

All patients received neoadjuvant, concurrent, and adjuvant chemo-hormonal therapy with nonstandardized regimens. We analyzed the prostate-specific antigen (PSA) response to neoadjuvant ADT, defined as the last documented PSA before the first RT treatment. Potential termination of adjuvant ADT was determined case-by-case for patients who achieved undetectable PSA after PDRT + ORT. Continuous ADT was given to those who did not achieve undetectable PSA, or per physician/patient preference. If adjuvant ADT was stopped, testosterone normalization was defined as the first date when values were above 150 ng/dL.

Radiation therapy

PDRT was performed using several modalities determined by the treating radiation oncologist. We included patients who received external beam radiation therapy (EBRT) or a combination of brachytherapy plus EBRT. Treatment to pelvic nodes was nonstandardized, though our typical fields extend from the aortic bifurcation distally through the obturator chains.

Outcomes and statistics

Outcomes were analyzed from the start of PDRT + ORT. PSA nadir was defined as the lowest PSA after PDRT + ORT before any local or distant failure. Biochemical recurrence (BCR) was defined using Phoenix criteria (nadir + 2).²⁴ Castrate resistance (CR) was defined per standard criteria with castrate testosterone

defined as ≤ 50 ng/dL.²⁵ Local failure (LF) was radiographic evidence of progression either within the prostate or treated metastasis and did not require pathologic confirmation. Distant metastatic progression (DMP) was radiographic development of new metastatic lesion(s) outside of the PDRT + ORT fields.

Follow-up was calculated using the reverse Kaplan-Meier method and was 27 months (95% confidence interval [CI], 16–42).²⁶ For outcome analyses, patients alive at last follow-up were censored. BCR, CR, and LF in the prostate or targeted metastases and DMP were measured until respective event, with death treated as a competing risk. All outcomes were calculated per patient except for targeted oligometastatic LF, which was calculated per metastasis. We used the Kaplan-Meier method to estimate OS and cumulative incidence using competing risks methodology to estimate all other events.

Univariable associations with outcomes were assessed using Cox regression and competing risks regression where appropriate. Outcomes with at least 10 events were assessed in relation to covariates. An undetectable PSA after PDRT + ORT, defined as <0.05 ng/dL, was assessed 2 ways: as a landmark analysis at 6 months post-RT for illustration purposes or as a time-dependent covariate for tests of association. Univariable associations with undetectable PSA 6 months after PDRT + ORT were assessed with Fisher exact test and Wilcoxon rank sum test.

Two-sided *P* values $< .05$ were considered significant, and all analyses were performed using SAS 9.4 TS1M6 (The SAS Institute, Cary, NC).

Results

Cohort characteristics

We identified 47 patients with DNOPC who were treated comprehensively with PDRT + ORT. Demographic and clinical characteristics are described in [Table 1](#). Cohort heterogeneity reflects the lack of an established standard of care for DNOPC and evolving institutional practice patterns over this period. All patients had adenocarcinoma histologically confirmed by our pathologists. Four (9%) patients had other high-risk features; specifically, 2 had intraductal features, 1 had neuroendocrine features, and 1 had both.

Distribution of treated oligometastases

Patients were predominantly M1b (92%) and received PDRT + ORT to 1 to 6 metastases either concurrently ($n = 37$; 79%) or sequentially with no intercurrent treatments besides ADT ($n = 10$; 21%). Of the 47 patients, 86 total oligometastases were treated. Twenty-one patients

Table 1 Patient characteristics

	n (%)
Total no. patients	47
Age at diagnosis, years	
Median (IQR)	67 (63-72)
Gleason score	
6	1 (2.1)
7	5 (10.6)
8	15 (31.9)
9	23 (48.9)
10	1 (2.1)
Unknown	2 (4.3)
Pretreatment PSA	
Median (IQR)	16.7 (6.7-44.9)
<20	28 (59.6)
≥20	19 (40.4)
High-risk histologic features (neuroendocrine and/or intraductal)	
Yes	4 (8.5)
No	43 (91.5)
Radiographic T-Stage	
T2b	4 (8.5)
T2c	5 (10.6)
T3a	11 (23.4)
T3b	20 (42.6)
T4	7 (14.9)
N-stage	
N0	21 (44.7)
N1	26 (55.3)
M-stage	
M0	1 (2.1)
M1a	2 (4.3)
M1b	43 (91.5)
M1c	1 (2.1)
Percent positive biopsy cores	
>50%	26 (55.3)
≤50%	12 (25.5)
Unknown	9 (19.1)
Metastasis classification	
Neighboring osseous only	26 (55.3)
Neighboring and non-neighboring osseous	9 (19.1)
Non-neighboring osseous only	7 (14.9)
Other	5 (10.6)
Number of targeted oligometastases	
Single	21 (44.7)
Multiple (2-6)	26 (55.3)
Chemo-hormonal therapy	
LHRH agonist/antagonist	47 (100.0)
Plus bicalutamide	5 (10.6)
Plus abiraterone	12 (25.5)
Plus enzalutamide	1 (2.1)
Plus docetaxel	2 (4.3)

Abbreviations: IQR = interquartile range; LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen.

fluorodeoxyglucose, PSMA, and sodium fluoride tracers, respectively.

Nearly 90% of treated sites were bone metastases. Neighboring bone metastases were twice as common and 55% initially presented with neighboring metastatic disease alone. The most common non-neighboring osseous sites were the spine and ribs, together accounting for 84% of irradiated distant osseous sites (Fig E1). The remaining 9 treated oligometastases were nodal or soft tissue. One patient with N1M0 disease received SBRT to an isolated iliac node; the remaining adenopathy was retroperitoneal or inguinal.

Hormonal and systemic therapy

The median duration of neoadjuvant ADT before start of RT was 26 weeks (interquartile range, 18-39 weeks). Table 1 details initial chemo-hormonal regimens. All patients received ADT with a luteinizing hormone-releasing hormone agonist or antagonist. In response to favorable data from STAMPEDE and the Phase III Abiraterone Acetate plus Prednisone in Patients with Newly Diagnosed High-risk Metastatic Castration-sensitive Prostate Cancer (LATITUDE) study, our institutional practice has shifted toward early integration of abiraterone; 26% of patients received this agent, all diagnosed between 2016 and 2018.^{27,28}

Radiation therapy treatment

There were several feasible treatment strategies used. Some patients received PDRT + ORT integrated in the same treatment, whereas others had step-wise treatments stretching over several months, with reassessment at each transition to confirm continued biochemical stability.

PDRT

PDRT was delivered using several modalities and fractionation schemes determined at the discretion of the treating radiation oncologist (Table 2). Most patients (n = 38; 81%) were treated using exclusively EBRT with relatively even distribution between conventionally, moderately hypofractionated, and extreme hypofractionated (ie, SBRT) regimens.

The remaining 9 patients (19%) underwent combination brachytherapy followed by EBRT. Of this group, 6 received high-dose-rate (HDR) brachytherapy to 1500 cGy delivered in a single fraction, and 3 patients received low-dose rate brachytherapy to a dose of 10,000 cGy using palladium-103 seeds. Postbrachytherapy, EBRT doses to the prostate and pelvic nodes were either 2500 cGy in 5 fractions (n = 3) or 4500 cGy in 25 fractions (n = 6).

(45%) were treated to a single oligometastatic site and the others were treated to multiple oligometastases. Baseline PET staging was performed in 10, 2, and 2 patients with

Table 2 RT treatment characteristics

RT component	Fractionation approach	Dosing	n (%)
PDRT			
	External beam-only approach		38 (81%)
	Conventional fractionation	180 cGy × 42-45	15 (32%)
	Moderate hypofractionation	270 cGy × 26	12 (26%)
	SBRT	700-800 cGy × 5	11 (23%)
	Brachytherapy plus EBRT combination		9 (19%)
	HDR brachytherapy combo	1500 cGy (HDR) plus 180 cGy × 25 or 500 cGy × 5	6 (13%)
	LDR brachytherapy combo	10,000 cGy (LDR) plus 180 cGy × 25 or 500 cGy × 5	3 (6%)
Nodal RT			
	Conventional fractionation	180 cGy × 25-26	24 (51%)
	SBRT regimen	500 cGy × 5	7 (15%)
	No nodal RT		15 (32%)
	Lymphadenectomy		1 (2%)
ORT (per patient; n = 47)			
	SBRT to all metastases		27 (57%)
	MH to all metastases		7 (15%)
	Conventional fractionation to all metastases		5 (11%)
	Mix of SBRT and MH		7 (15%)
	Mix of SBRT and conventional fractionation		1 (2%)
ORT (per lesion; n = 86)			
	SBRT regimens		53 (62%)
	Single fraction	2400 cGy × 1	7 (8%)
	3-fraction regimen	800-900 cGy × 3	26 (30%)
	5-fraction regimen	450-800 × 5	16 (19%)
	6-fraction regimen	600 cGy × 6	4 (5%)
	Moderate hypofractionation	220-270 cGy × 25-26	22 (26%)
	Conventional fractionation	180-200 cGy × 23-39	11 (13%)

Abbreviations: EBRT = external beam radiation therapy; HDR = high-dose rate; LDR = low-dose rate; MH = moderate hypofractionation; ORT = oligometastasis-directed radiation therapy; PDRT = prostate-directed radiation therapy; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Pelvic nodal treatment

Thirty-one patients (66%) received full pelvic nodal RT using 1 of several dose regimens (typically 180 cGy for 25-26 fractions or 500 cGy for 5 fractions). Eleven (23%) patients with radiographic suspicion of N1 disease received an RT boost to grossly positive nodes, as our institutional practice is to boost using intensity modulated RT dose painting to a total dose of 5625 cGy in 25 fractions. One patient underwent pelvic lymphadenectomy given uncertainty over disease involvement.

ORT

Oligometastases were treated heterogeneously, and the selection of the specific dose used was dependent on anatomic location and PDRT dose (Table 2). Fifty-three lesions (62%) were treated with hypofractionation in 6 treatments or less, most often to 27 Gy in 3 fractions, which is our institutional oligometastasis standard.²⁹ Typical SBRT treatment plans included a direct expansion from gross tumor volume to planning tumor volume depending on anatomy. When possible, regional osseous or nodal metastases were incorporated into broader PDRT fields to minimize treatment time and were thus treated

with moderately hypofractionated or conventional doses (Fig 1). For patients who received moderately hypofractionated PDRT, doses to incorporated regional metastases ranged from 55 to 70.2 Gy.

Treatment outcomes

By the end of follow-up, 7 patients had died and median OS was not reached (Fig 2A). The 2-year OS was 86.6% (95% CI, 67.7%-94.7%), and the cause of death was suspected to be mPC for all but 1 patient. DMP occurred in 15 patients with 1- and 2-year cumulative incidences of 20.9% (95% CI, 10.1%-34.2%) and 31.5% (95% CI, 16.8%-47.3%), respectively (Fig 2B). Table 3 shows univariable associations with DMP. Neuroendocrine/intraductal histology had significantly greater risk of DMP (hazard ratio [HR], 4.56; 95% CI, 1.55-13.46; *P* = .006). Patients with an initial PSA > 20 had a lower hazard of DMP (HR, 0.33; 95% CI, 0.11-0.99; *P* = .049), as did those who achieved undetectable PSA post-PDRT + ORT when treated as a time-dependent covariate (HR, 0.26; 95% CI, 0.08-0.84; *P* = .025). No other factors

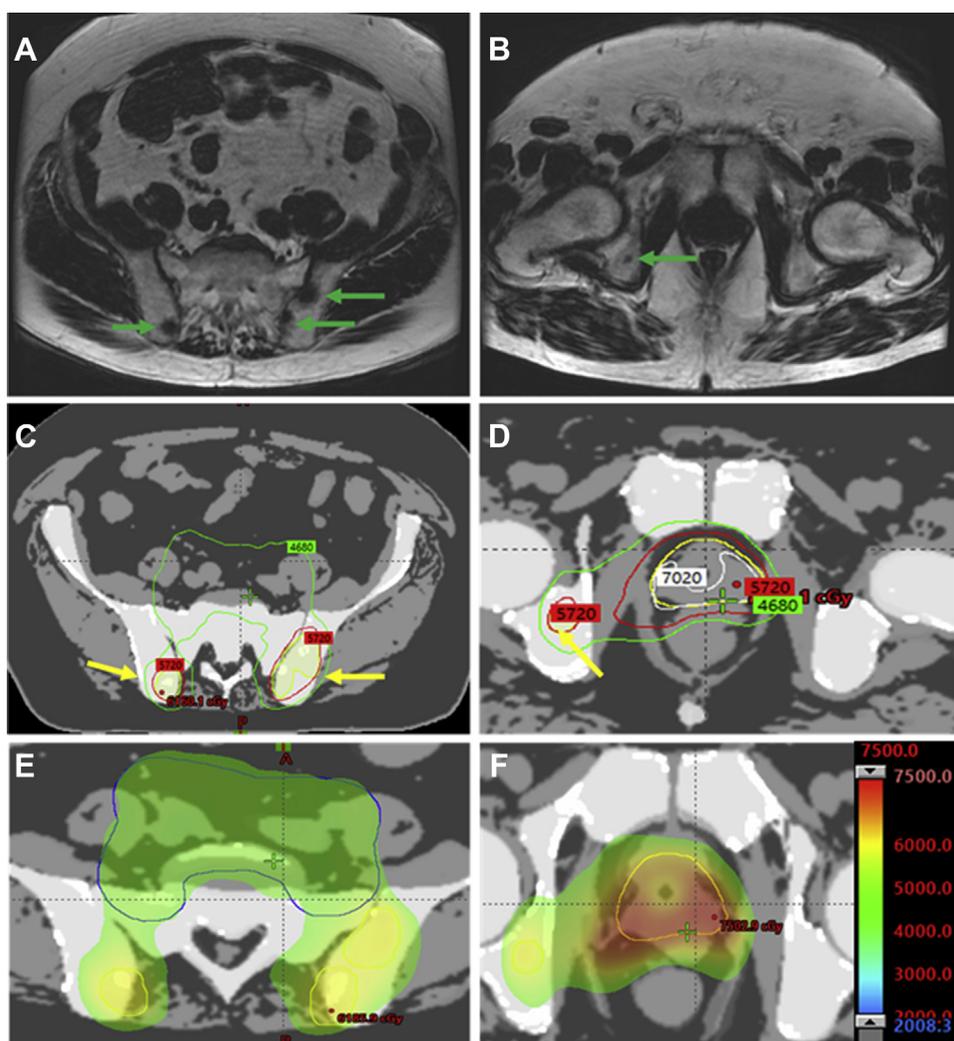


Figure 1 Representative dosimetry for patients with de novo oligometastatic prostate cancer (DNOPC) treated to regional metastases. This 68-year-old man was diagnosed with radiographic T3aN1M1b Gleason 4 + 5 adenocarcinoma with evidence of 4 regional bony metastases on initial staging magnetic resonance imaging (MRI) (A and B, green arrows). He was treated with moderate hypofractionation to the prostate (7020 cGy) and pelvic nodes (4860 cGy) using intensity modulated radiation therapy (IMRT). Treatment fields were modified to include the regional bone metastases (C and D, yellow arrows), which were dose painted to 5720 cGy. Panels E and F show a zoomed-in color wash view.

were significantly associated with DMP, including number/distribution of metastases.

Local prostate relapse was rare, with only 3 suspected cases. Local control of treated oligometastases was also excellent. In total, 10 targeted oligometastases progressed, corresponding to a 2-year cumulative incidence of 12.9% (95% CI, 5.9%-22.8%). All but 2 metastases that progressed were osseous; the sample size was not sufficient to assess for associations with specific ORT fractionations.

Biochemical response

After neoadjuvant ADT, but prior to PDRT + ORT, a total of 9 patients (19%) achieved undetectable PSA. By 6 months after PDRT + ORT, 27 patients (57%) were

undetectable and in total, 32 patients (68%) ultimately achieved undetectable PSA at any point after PDRT + ORT. We next examined univariable associations with undetectable PSA 6 months after PDRT + ORT. A higher proportion of undetectable patients received abiraterone ($n = 10$; 37%) compared with detectable patients ($n = 2$; 10%; $P = .047$). Undetectable patients trended toward lower pretreatment PSA (median: 13.6 ng/mL vs 22.9 ng/mL; $P = .07$) and older age (median: 69 vs 66 years; $P = .09$).

Twelve patients experienced BCR with 1- and 2-year cumulative incidences of 10.0% (95% CI, 3.1%-21.8%) and 22.5% (95% CI, 10.2%-37.6%), respectively (Fig 3A). Development of CR occurred in 16 patients, with 1- and 2-year cumulative incidences of 19.2% (95% CI, 8.8%-32.6%) and 36.2% (95% CI, 20.1%-52.6%),

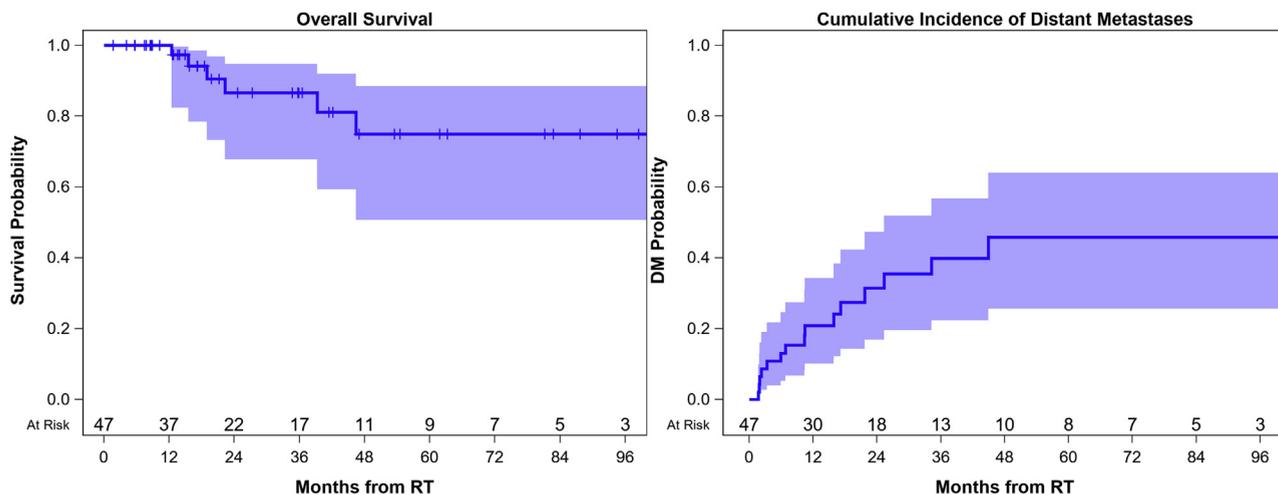


Figure 2 Kaplan-Meier curve for the full cohort showing (A) overall survival (OS) and (B) cumulative incidence of distant metastatic progression (DMP) after prostate-directed radiation therapy (PDRT) + oligometastasis-directed radiation therapy (ORT).

respectively (Fig 3B). Again, when treated as a time-dependent covariate, undetectable PSA after PDRT + ORT was prognostic of a lower hazard of both BCR (HR, 0.19; 95% CI, 0.06-0.59; $P = .004$) and CR (HR, 0.17; 95% CI, 0.04-0.64; $P = .009$) (Table E1). When landmarked at 6 months, undetectable PSA after PDRT + ORT had significantly lower cumulative incidence of BCR (6.3% vs 37.5% at 2 years postlandmark; $P = .04$; Fig 3C); however, this was not the case for DMP (20.8% vs 32.6% at 2 years postlandmark; Fig 3D).

In total, 23 (49%) patients discontinued adjuvant ADT; all but 3 of these patients had undetectable PSA when ADT was stopped, and the remaining 3 stopped because of personal preference. At analysis, 16 (70%) of these 23 patients had testosterone recovery of which 5/16 (31%) then had subsequent PSA rise and restarted ADT 2 to 21 months postrecovery. The remaining 11/16 (69%) patients remained off ADT without documented BCR; 9 patients had stable, low PSA, and 2 had rising PSA without biochemical or radiographic relapse. Across the 16 patients, median noncastrate duration was 7.8 months and 7 of 16 (44%) had normalized testosterone for >12 months, highlighting the potential for meaningful remission with improved quality of life.

Discussion

This study describes a unique cohort of predominantly patients with M1b DNOPC who received an aggressive, upfront strategy with neoadjuvant ADT followed by comprehensive RT to all gross disease. The clinical importance is underscored by the projected increased prevalence of DNOPC. Several epidemiologic studies suggest that the overall incidence of mPC is rising,^{30,31} and increased adoption of sensitive functional imaging

like PSMA PET may enhance detection of previously occult low-volume metastases.^{32,33}

Posttreatment, there were no standardized ADT discontinuation criteria; therefore, outcomes were blended across a population containing both continuous and limited adjuvant ADT. Despite the heterogeneity, we believe PDRT + ORT offers the possibility of noncastrate remissions with improved quality of life for a subset of treated patients, as the median period with normalized testosterone was nearly 8 months.

PDRT + ORT has excellent local control as expected from prospective SBRT trials^{20,21}; however, there remains a modest risk of DMP. Although limited by sample size and follow-up, intraductal/neuroendocrine histology and detectable posttreatment PSA were associated with increased hazard of DMP. There was a signal that achieving undetectable PSA after PDRT + ORT is important; when treated as a time-dependent covariate, it prognosticated reduced risk of BCR and DMP. However, when landmarked at 6 months, it was no longer significantly associated with DMP due to relatively numerous early DMP events, which were excluded within the landmark time. Further work is necessary to better identify patients with DNOPC who have a greater propensity for early progression and are less likely to benefit from PDRT + ORT.

We also report a seemingly paradoxical association where those with initial PSA > 20 had reduced DMP risk. This finding contradicts other metastatic series associating initial PSA > 20 with poorer outcomes.^{34,35} Several factors might be contributing. First, mean duration of neoadjuvant ADT in patients who had PSA > 20 was longer, and this incremental exposure might have reduced subsequent DMP. Second, all 4 high-risk histology patients had initially low PSA and 3/4 had subsequent DMP. Third, given that only patients who successfully received

Table 3 Univariable associations with DMP

	Distant metastases			
	n (DMP events)	HR	[95% CI]	P value
Age at diagnosis, years	47 (15)	1.07	[0.98 -1.16]	.11
Pretreatment PSA				
≥ 20	19 (4)	0.33	[0.11-0.99]	.049
<20	28 (11)	—		
Gleason score				
>7	39 (13)	2.09	[0.25-17.15]	.49
≤ 7	6 (1)	—		
Any Gleason 5				
Yes	24 (7)	1.09	[0.40-2.96]	.86
No	21 (7)	—		
High-risk histologic features (neuroendocrine and/or intraductal)				
Yes	4 (3)	4.56	[1.55-13.46]	.006
No	43 (12)	—		
Percent positive cores	38 (10)	0.84	[0.07-10.24]	.89
Percent positive cores				
>50%	26 (7)	0.99	[0.26-3.78]	>.95
≤ 50%	12 (3)	—		
T-stage				
T3-T4	38 (13)	1.62	[0.34-7.70]	.54
T2	9 (2)	—		
Number of targeted metastases				
Multiple	26 (10)	1.69	[0.58-4.86]	.33
Single	21 (5)	—		
Metastasis RT approach				
SBRT	27 (8)	0.70	[0.25-1.96]	.50
All others	20 (7)	—		
Prostate RT approach				
All others	27 (9)	—		
SBRT/brachy	20 (6)	1.02	[0.37-2.80]	>.95
N-stage				
N1	26 (8)	0.82	[0.30-2.25]	.70
N0	21 (7)	—		
Nodal RT boost				
Yes	11 (3)	1.36	[0.35-5.33]	.66
No	35 (12)	—		
Abiraterone given as part of ADT				
Yes	12 (2)	0.91	[0.19-4.32]	.90
No	35 (13)	—		
PSA undetectable post-ADT				
Yes	9 (1)	0.29	[0.05-1.58]	.15
No	38 (14)	—		
PSA undetectable 6 mo post-PDRT + ORT (landmarked)				
Yes	27 (6)	0.87	[0.24-3.16]	.83
No	20 (9)	—		
PSA undetectable post-PDRT + ORT (time dependent covariate)				
Yes		0.26	[0.08-0.84]	.025
No		—		
ADT duration, weeks	47 (15)	1.01	[0.97-1.05]	.72

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; DMP = distant metastatic progression; HR = hazard ratio; ORT = oligometastasis-directed radiation therapy; PDRT = prostate-directed radiation therapy; PSA = prostate-specific antigen; RT = radiation therapy; SBRT = stereotactic body radiation therapy.

Bold values indicate significant value with $P < .05$.

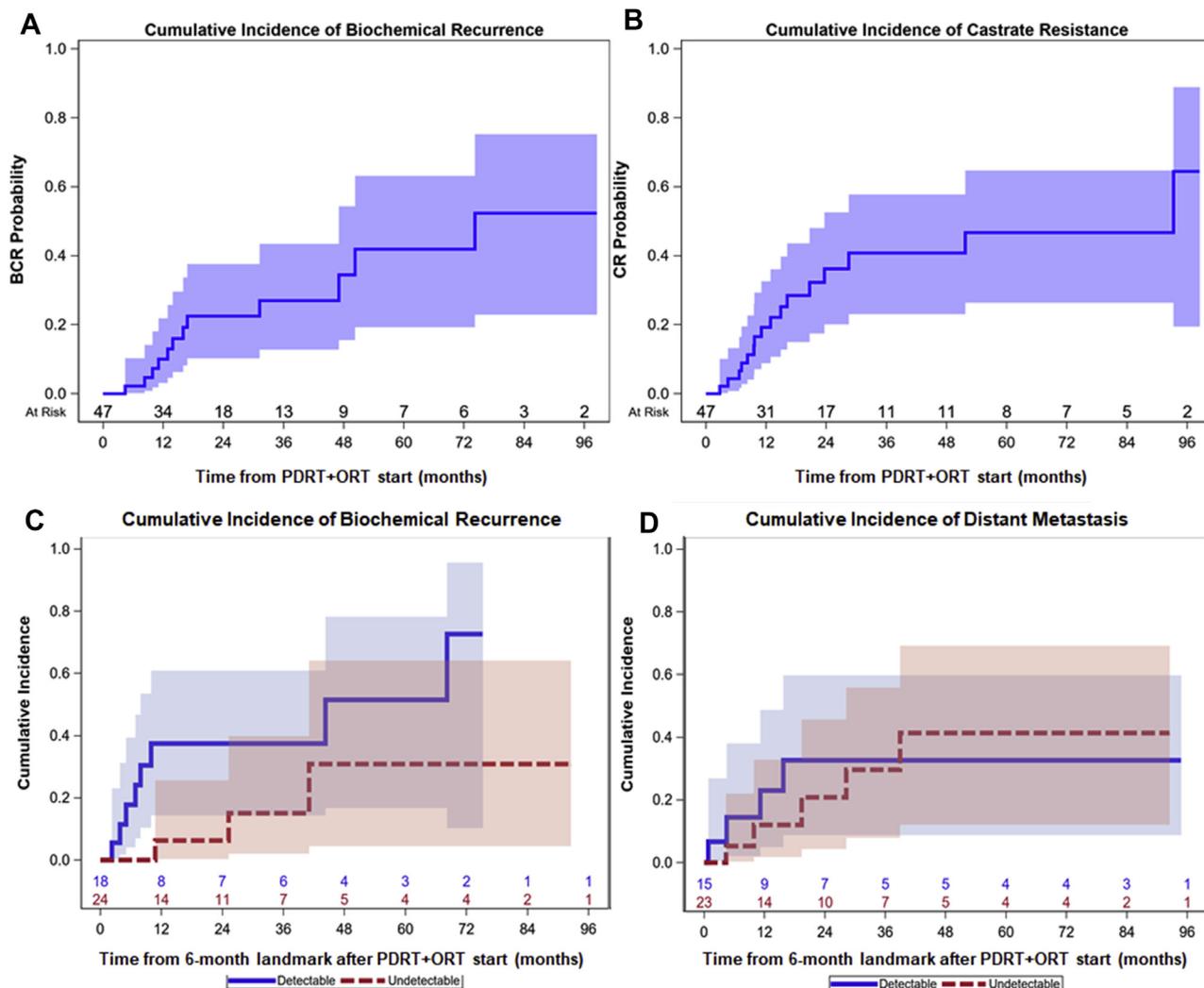


Figure 3 Cumulative incidence curves for (A) biochemical recurrence (BCR) (by Phoenix definition) and (B) castrate resistance (CR) after prostate-directed radiation therapy (PDRT) + oligometastasis-directed radiation therapy (ORT) in addition to (C) cumulative incidence of BCR and (D) distant metastatic progression (DMP) stratified by those patients who achieved undetectable prostate-specific antigen (PSA) landmarked at 6 months postcompletion of PDRT + ORT.

PDRT + ORT were included, there may have been selection bias for more indolent PSA > 20 patients. Patients whose disease progressed post-ADT would have been unlikely to be referred for PDRT. The last explanation is a potential false positive finding given our limited sample size.

For many, prostatectomy or PDRT are both suitable options. There have been several single-institutional series that demonstrate potential benefits for prostatectomy in the oligometastatic setting but caution the importance of patient selection.³⁶⁻³⁹ The prospective HORRAD¹⁶ and STAMPEDE¹⁸ trials strengthened the foundation for PDRT in patients with metastatic and particularly oligometastatic cancers. There are, however, minimal comparative data on the outcomes of patients with

oligometastatic disease who receive comprehensive PDRT + ORT.

At our institution, a pilot prospective study was conducted in 20 patients with M1a or M1b disease who received multimodal treatment including ADT, radical prostatectomy, and lymphadenectomy plus SBRT to osseous metastases.²³ Overall, 95% achieved undetectable PSA, with 25% after upfront ADT, 50% after surgery, and 20% after SBRT, suggesting that all modalities contributed. The primary endpoint, undetectable PSA after testosterone recovery, was achieved by 20%, and 2 patients had long-term remissions. These results agree with the findings here that a small proportion of patients may gain durable responses from intensive local therapies.

Tsumura et al³⁵ evaluated 40 patients with N1M0 (n = 22), M1a (n = 3), or M1b (n = 15) who received neoadjuvant ADT followed by HDR brachytherapy (37.5 Gy). Patients with M1a/M1b disease also received 30 Gy prostate EBRT, whereas those with N1M0 underwent 40 Gy whole pelvis EBRT. All patients then received 36 months of adjuvant ADT. Nine N1M0 patients and 9 N0M1b patients also received MDT as a 10-Gy nodal boost or 30 to 50 Gy to bone metastases, respectively. Overall, they reported a 5-year CR-free survival and cancer-specific survival of 64% and 88%, respectively. Compared with patients who underwent PDRT alone, those who had MDT had significantly improved CR-free survival (HR, 0.32; 95% CI, 0.12-0.88) and improved chance of achieving undetectable PSA posttreatment. Although intriguing, it is challenging to interpret these data given that patients with N1M0 likely drove a large portion of the effect. Of note, neither subgroup (N1M0 or M1b) had independently significantly improved CR-free survival.

Riva et al,⁴⁰ who reviewed 20 patients with DNOPC who received neoadjuvant ADT followed by PDRT, found an early signal of improved control versus ADT alone. Although many received MDT to some bone metastases, these data are not immediately comparable because most did not receive comprehensive ORT.

Recently, Deantoni et al⁴¹ reported on a cohort of 39 patients presenting with bone-only DNOPC who received simultaneous RT to the prostate (54%) or prostate bed (46%) and 1 to 2 bone metastases with long-course ADT. With median follow-up of 42 months, they reported that 19/41 had undetectable PSA (all of whom remained on ADT). Similar to our findings, there was a small cohort (n = 5) of patients off ADT and free of BCR, suggesting that total consolidation RT warranted further study.

Several prospective trials should clarify the utility of an intensive multimodal approach. The STAMPEDE trial plans to assess the incremental benefit of MDT to PDRT or prostatectomy and a SWOG phase III trial will compare standard systemic therapy with prostatectomy or PDRT, during which patients with DNOPC may receive MDT to ≤ 4 sites prerandomization.⁴² A phase II protocol for M1a or M1b disease with 1 to 5 metastases will study 6 months of escalated ADT with leuprolide, abiraterone, and apalutamide with radical prostatectomy +/- postoperative RT and SBRT to metastases.⁴³ The Randomized Feasibility Trial of Prostate Radiotherapy vs Prostatectomy in Men with Hormone Sensitive Oligometastatic Prostate Cancer (PRORAD) trial will randomize patients to either RP versus HDR or SBRT plus intermittent ADT and SBRT to all metastases.⁴⁴ Finally, the Metacure trial will evaluate the incremental benefit of intensified hormonal therapy with abiraterone and apalutamide with comprehensive RT.⁴⁵

We acknowledge several limitations of this study. First, we did not include ADT-alone or PDRT-alone patients and therefore cannot assess the incremental benefit

of PDRT + ORT. Second, there is potential selection bias of more favorable patients, as we only included those who successfully received definitive PDRT + ORT. Given this was retrospective and off protocol, there is inherent treatment heterogeneity including ADT duration/type and PDRT + ORT dose. Patients received several PDRT doses with differing radiobiologic equivalence; however, all are established curative regimens for patients with nonmetastatic cancer. Furthermore, comparability of hypofractionated and nonhypofractionated ORT dosing is challenging. Although numerous series demonstrate good outcomes for SBRT to treatment of prostate oligometastases, control rates with moderately hypofractionated or conventional doses are unknown.^{22,46,47}

Overall, this study highlights how DNOPC can be treated with RT and reflects evolving institutional practice patterns. In recent years, a greater proportion of our patients with nonmetastatic cancer have been treated with SBRT. Increasingly, PSMA PET is being used for baseline staging, which we speculate will become more common, given ORIOLE's discovery that men who received total SBRT consolidation to all baseline, PSMA-avid lesions had improved progression-free survival compared with incomplete SBRT (ie, select PSMA-avid lesions untreated).²¹ In our series, the limited upfront PSMA-staging makes it impossible to validate this finding but should be studied further. There was also diversity in the interval and imaging strategies used for posttreatment assessment. Given relatively few patients were surveilled with functional imaging, it is possible we are underestimating radiographic recurrence.

Although this is, to our knowledge, the largest study of PDRT + ORT patients reported, it remains small with relatively few events. Further work with larger cohorts and more homogenous treatments is necessary to detect associations with particular dosing schemes or chemo-hormonal durations/regimens. Intensified upfront ADT with abiraterone was associated with greater likelihood of achieving undetectable PSA at 6 months post-PDRT + ORT but was only received by one-quarter of patients. Two randomized trials have shown a benefit of abiraterone in the de novo metastatic setting.^{27,28} The OS advantage of upfront docetaxel might be confined to patients with more extensive metastases, though more recent data suggest all patients may benefit.⁴⁸⁻⁵¹ The optimal systemic therapy regimen for patients with DNOPC remains an area of significant debate and adding PDRT + ORT adds further complexity.⁵² Future studies will also be needed to better inform optimal patient selection.

Conclusions

Despite limitations, this study offers important, novel insights given a relative lack of data guiding RT approaches for this unique population. Given early

encouraging signals that PDRT + ORT may offer the possibility of meaningful noncastrate remissions for a subset, this is a promising strategy that warrants further prospective study.

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Supplementary data

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