Effect on Overall Survival of Locoregional Treatment in a Cohort of De Novo Metastatic Prostate Cancer Patients: A Single Institution Retrospective Analysis From the Royal Marsden Hospital

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Abstract

We retrospectively evaluated the effect of locoregional treatment (LRT) on overall survival (OS) in 300 metastatic at diagnosis (M1) prostate cancer patients. LRT was associated in univariate and multivariate analysis with longer OS, which remained significant for radiotherapy but not for transurethral prostatectomy. These data support further prospective evaluation of the benefit of local control in this patient population.

Background: The optimal management of the primary tumor in metastatic at diagnosis (M1) prostate cancer (PCa) patients is not yet established. We retrospectively evaluated the effect of locoregional treatment (LRT) on overall survival (OS) hypothesizing that this could improve outcome through better local disease control and the induction of an anti-tumor immune response (abscopal effect). **Patients and Methods:** M1 at diagnosis PCa patients referred to the Prostate Targeted Therapy Group at the Royal Marsden between June 2003 and December 2013 were identified. LRT was defined as either surgery, radiotherapy (RT) or transurethral prostatectomy (TURP) administered to the primary tumor at any time point from diagnosis to death. Kaplan–Meier analyses generated OS data. The association between LRT and OS was evaluated in univariate (UV) and multivariate (MV) Cox regression models. **Results:** Overall 300 patients were identified; 192 patients (64%) experienced local symptoms at some point during their disease course; 72 patients received LRT (56.9% TURP, 52.7% RT). None of the patients were treated with prostatectomy. LRT was more frequently performed in patients with low volume disease (35.4% vs. 16.2%; $P < .001$), lower prostate-specific antigen (PSA) level at diagnosis (median PSA: 75 vs. 184 ng/mL; $P = .005$) and local symptoms (34.2% vs. 4.8%; $P < .001$). LRT was associated in UV and MV analysis with longer OS (62.1 vs. 55.8 months; hazard ratio [HR], 0.74; $P = .044$), which remained significant for RT (69.4 vs. 55.1 months; HR, 0.54; $P = .002$) but not for TURP. RT was associated with better OS independent of disease volume at diagnosis. **Conclusion:** These data support the conduct of randomized phase III trials to evaluate the benefit of local control in patients with M1 disease at diagnosis.

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Introduction

The standard management of de novo metastatic prostate cancer (mPCa) has recently changed to combine docetaxel chemotherapy with androgen deprivation therapy (ADT) for fit patients.[1-3] Definitive treatment of the local prostate tumor in the form of surgery or radiotherapy (RT) is not generally contemplated for asymptomatic patients in the metastatic setting; rather it is usually reserved for patients with organ-confined or locally advanced prostate cancer (PCa). The role of locoregional treatment (LRT) such as surgery, RT, or transurethral prostatectomy (TURP) in mPCa is mostly used for the palliation of local symptoms such as hematuria or urinary obstruction, and its effect on overall survival (OS) remains undefined.

This treatment paradigm has been challenged by a growing body of evidence on the basis of several retrospective studies[4-8] suggesting a potential OS benefit from radical prostatectomy or RT for patients with mPCa at diagnosis. For several other malignancies, including colorectal, kidney, and ovarian cancer, maximal cytoreduction including removal of the primary tumor has been shown to provide an OS advantage.[9-13] In breast cancer, despite several retrospective series suggesting a similar favorable effect, a recently published randomized controlled trial failed to confirm such evidence.[14]

Besides the more intuitive rationale for treating the primary tumor, whereby the reduction of the overall tumor burden might limit the risk of metastatic spread, emerging preclinical evidence now supports a more aggressive treatment approach for the local prostate tumor even in the metastatic setting. The "tumor self-seeding theory" suggests that circulating tumor cells might spread and metastasize not only from the primary site to distant organs but also in the opposite direction, reinfiltrating the site of origin, which could become a reservoir of tumor cells with metastatic potential.[15] Moreover, LRT of the primary tumor could act as an effective endogenous vaccine through tumor antigen shedding, resulting in the regression not only of the directly treated local tumor but also of the distant metastatic sites through "abscopal effects".[16] RT-induced inflammation and tumor necrosis is also postulated to cause the acute release of multiple tumor-associated antigens, which in turn elicit a specific $CD8^+$ T-cell mediated antitumor immunological effect.[16] This secondary immunological response could potentially convert RT into a potent systemic treatment with unexplored clinical benefits, which go beyond mere local control or symptom palliation. Primary tumor-derived exosomes and cytokines have also been postulated to contribute to the creation of a receptive microenvironment ("pre-metastatic niche") for the subsequent development of metastatic sites in specific organs. It has been suggested that the untreated primary disease continues to affect the growth of the metastatic disease in an endocrine manner.[17]

Several ongoing large prospective phase II and III trials are investigating whether LRT should be recommended in mPCa patients (NCT01751438, NCT02138721, NCT01957436, NCT00268476). In the present study we aimed to determine the survival of patients who underwent LRT administered at any time point along the course of the disease in a retrospective study to evaluate a population of patients diagnosed with mPCa at presentation. Secondarily, we described the type and the incidence of local symptoms in this population, their management, and the treating physician's rationale for prescribing LRT.

Patients and Methods

Study Population and Data Collection

Prostate cancer patients with metastatic disease at diagnosis referred to the Prostate Targeted Therapy Group at the Royal Marsden NHS Foundation Trust between June 2003 and December 2013 were selected. The time of data cutoff was January 16, 2016. Clinical patient data were collected from the Electronic Patients Record. Variables including age, diagnostic Gleason score, Eastern Cooperative Oncology Group (ECOG) performance status (PS) at diagnosis or first referral, post castration-resistant PCa (CRPC) lines of standard therapies received, prostate-specific antigen (PSA) level at diagnosis, metastatic sites, and volume of disease at diagnosis or first referral and at the time of LRT, were retrospectively recorded. Information on local symptoms (pelvic pain, hematuria, urinary frequency, urinary retention, hydronephrosis), intervention (medications, TURP, surgery, RT, cystoscopy, suprapubic catheterization, ureteric stenting, hospitalization, and catheterization) at diagnosis and/or at any time point along the course of the disease; the physician decision rationale and treatment intent for LRT were also collected.

Locoregional treatment was defined as the receipt of treatment to the primary tumor consisting of either surgery (radical prostatectomy), RT (administered at any dose and fractionation), or TURP at any time point along the disease course from diagnosis to death. The volume of disease was classified according to ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease (CHAARTED) criteria[1] into high (presence of visceral metastases or ≥ 4 bone lesions of which at least 1 beyond the vertebral bodies and pelvis) or low volume (< 4 bone lesions without visceral metastases). The intent of RT was categorized as either palliative (palliation of local symptoms) or radical (definitive local RT only or in combination with external beam radiation therapy [EBRT] directed to the metastatic sites in the context of oligometastatic or oligorecurrent disease).[18]

Statistical Analysis

A descriptive analysis of clinical variables was performed. Categorical variables were presented as proportions (%) and continuous variables were presented by the median values with interquartile range. Differences in baseline variables between groups of those who received LRT and those who did not receive LRT were evaluated using χ^2 (categorical values) and Student t tests (continuous variables).

Median survival values for each of the groups were calculated using Kaplan–Meier analyses. The association of LRT with survival was evaluated in univariable and multivariable Cox regression models. Variables in the multivariable model included LRT, age, PSA (log-transformed), Gleason score, tumor volume, and the presence of symptoms. Cox regression models were estimated for LRT (RT and surgery) and for RT and surgery and LRT separately. Only P values $< .05$ were considered statistically significant. No correction for multiple testing was performed.

Results

Patient Characteristics and Local Symptoms

Overall 300 PCa patients with metastatic disease at diagnosis were identified. Patient characteristics at diagnosis or first referral are summarized in Table 1. Most patients (95.6%) presented with good baseline ECOG PS (0 or 1) and received a median of 3 lines of treatment for metastatic CRPC. In total 192 patients (64%) experienced local symptoms at some point during their disease course with 99 patients (33%) having these at diagnosis and 148 patients (49.3%) developing symptoms later on during the course of the disease. Clinical data on local symptoms during the course of the disease were not available in 4 of the 192 symptomatic patients.

Follow-up of these local symptoms in the 99 patients who were symptomatic at diagnosis indicated that 42 of these patients (42 of 99; 42.4%) did not report any further local symptoms during the course of the disease of whom only 20 had received a specific intervention for their local symptoms. Fifty-three patients (53 of 99; 53.5%) continued to experience local symptoms with 19 reporting the same (19 of 53; 35.8%), 32 worsening (32 of 53; 60.3%), and 2 improving local symptoms (2 of 53; 3.7%). Follow-up data on these local symptoms were not available for 4 patients. Of the 99 patients who presented with local symptoms at diagnosis, 44 patients (44.4%) received medical intervention to manage their local symptoms whereas 55 patients (55.5%) did not. In the 44 patients who received medical intervention, local symptoms resolved during the course of the disease in 19 (19 of 44; 43.1%), improved in 3 (3 of 44; 6.8%), and persisted or worsened in 18 patients (18 of 44; 40.9%).

Urinary frequency was the most commonly reported symptom at diagnosis (20%), followed by urinary retention (7.3%), hematuria (4.3%), pelvic pain (4%), and hydronephrosis (2%; Table 2). During the course of the disease, urinary frequency remained the most frequently reported local symptom (37.7%) followed by pelvic pain (12.7%), urinary retention (12%), hematuria (11%), and hydronephrosis (8.7%).

Table 1 Patient Characteristics

	All Patients	LRT	No LRT
Median Age (Range), y	63 (57.7-68.5)	62.2 (56.9-66.5)	63.1 (57.8-68.6)
ECOG PS, n (%)			
0-1	287 (95.7)	64 (92.8)	217 (96.4)
2	13 (4.3)	5 (7.2)	8 (3.6)
Mean PSA (Range), (ng/mL)	150 (55-500)	75 (35-381)	184 (65.3-533.5)
Gleason Score, n (%)			
≥8	164 (54.7)	44 (63.8)	116 (51.6)
<8	66 (22)	16 (23.2)	49 (21.8)
Unknown	70 (23.3)	9 (13)	60 (26.7)
Metastatic Sites, n (%)			
Bone	265 (88.3)	54 (78.3)	207 (92)
Lymph nodes	83 (27.7)	23 (33.3)	56 (24.9)
Visceral	15 (5)	4 (5.8)	11 (4.9)
Tumor Burden (CHAARTED Criteria), n (%)			
High	181 (60.3)	29 (42)	150 (66.7)
Low	117 (39)	40 (58)	73 (32.4)
Mean Post-CRPC Lines of Treatment (Range), n	3 (2-3)	3 (2-3)	3 (2-3)

Abbreviations: CHAARTED = ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; LRT = locoregional treatment; PS = performance status; PSA = prostate-specific antigen.

Locoregional Treatment

Overall 72 patients (24%) received LRT to the primary tumor (Table 3);18 (25%) received this at diagnosis and 54 (75%) later during the course of the disease. Of these, most were symptomatic with only 13 (18%) being free of local symptoms from the primary tumor at the time LRT was performed. For those who received LRT during the course of the disease, median time from diagnosis to LRT was 41.6 (range, 6.9-170.1) months.

The most common form of LRT was TURP in 41 patients (56.9%) followed by RT in 38 patients (52.7%); 8 patients (11.6%) underwent TURP as well as RT; 1 patient (1.4%) had focal surgical intervention (laser prostatectomy) but none of the patients received radical prostatectomy.

All patients treated with TURP reported local symptoms at the time of treatment; 15 patients (38.5%) had a TURP performed at diagnosis and 26 patients (63.4%) later during the course of treatment. For those treated during the course of the disease, median time from diagnosis to TURP was 38.9 months (range, 8-119 months).

Of those treated with RT, 63.2% were symptomatic from the local tumor at the time of local RT; 5 patients (13.2%) received RT at diagnosis and 33 patients (86.8%) later during the course of the disease. In those treated during the course of the disease, median time from diagnosis to RT was 46.7 (range, 6.9-170.1) months. Among these 33 patients treated with local RT along the disease course, 24 patients were symptomatic from the local tumor at the time of administration of RT. After local irradiation, local symptoms improved or resolved in 12 patients (12 of 24; 50%) but persisted or worsened in the other 12 patients (12 of 24; 50%). Of the 156 patients with local symptoms but not treated with RT, 27 patients (17.3%) required multiple treatments to control local progression.

Radiotherapy with radical intent was administered to the primary tumor to 16 patients (42.1%) with oligometastatic or oligorecurrent disease[18] of whom 8 patients were treated with synchronous EBRT to additional bone or nodal metastatic lesions. Twenty-one patients (55.3%) received RT with the intent to palliate local symptoms or improve the local control of the disease. Data on 1 of these patients were missing. Twenty-six patients (76.5%) received at least 30 Gy, and 6 patients (15.8%) were treated with doses of 60 Gy or higher; the dose was unknown in 4 patients (10.5%) and fractionation was inconsistently reported.

Locoregional treatment was more frequently performed in patients with low-volume metastatic disease (35.4% vs. 16.2%; $P < .001$), lower PSA level at diagnosis (median PSA: 75 vs. 184 ng/mL; $P = .005$), and with local symptoms (34.2% vs. 4.8%; $P < .001$). No significant association was found with age (median age: 63.1 vs.

Table 2 Local Symptoms

	All Patients (n = 294)		LRT (n = 69)		No LRT (n = 225)	
	At Diagnosis	During Disease	At Diagnosis	During Disease	At Diagnosis	During Disease
At Least 1 Symptom	96 (32)	147 (49.3)	32 (46.4)	56 (81.2)	60 (26.7)	91 (40.4)
Pelvic Pain	12 (4)	38 (12.7)	4 (5.8)	14 (20.3)	6 (2.7)	23 (10.2)
Hematuria	13 (4.3)	33 (11)	4 (5.8)	18 (26.1)	9 (4)	14 (6.2)
Urinary Frequency	60 (20)	113 (37.7)	17 (24.6)	42 (60.9)	41 (18.2)	71 (31.6)
Urinary Retention	22 (7.3)	36 (12)	11 (15.9)	18 (26.1)	9 (4)	18 (8)
Hydronephrosis	6 (2)	26 (8.7)	3 (4.3)	18 (26.1)	3 (1.3)	8 (3.6)

Data are presented as n (%). Information on symptoms was missing for 6 patients (2%).
Abbreviation: LRT = locoregional treatment.

62.2 years; $P = .409$) or Gleason Score ≥ 8 (24.6% vs. 27.5%; $P = .657$). The pattern of metastatic spread was not clearly associated with LRT. Although there was a nonsignificant trend toward patients with lymph node-only disease receiving LRT in higher proportion (37% vs. 21.5%; $P = .068$), no differences were observed in patients with visceral (22.7% vs. 26.7%; $P = .725$) or bone-only (28.7% vs. 20.5%; $P = .125$) metastases.

Survival

Median follow-up was 54.6 (range, 11.9-227.8) months, with 266 (88.7%) deaths. Median OS for the whole cohort was 57.9 months (95% confidence interval, 51.9-63.9; Figure 1A). In univariate analysis, LRT was associated with better OS (62.1 vs. 55.8 months; hazard ratio [HR], 0.74; $P = .044$). LRT was also associated with improved survival in a multivariable model including age, Gleason Score, PSA, volume of disease (low vs. high) at diagnosis and presence of symptoms as covariates (Table 4, section A). We then evaluated whether the type of LRT (RT or TURP/surgery) would have an equivalent effect on OS. In univariate analysis, TURP/surgery was associated with a nonsignificant decrease in OS (54.3 vs. 58.8 months; HR, 1.23; $P = .239$) (Figure 1B), whereas patients who received local RT appeared to have a significant OS advantage (69.4 vs. 55.1 months; HR, 0.54; $P = .002$; Figure 1C), which was maintained in the multivariable Cox regression model (Table 4, section B). There was no significant interaction between RT treatment administration and disease volume evaluated at diagnosis or first referral (CHAARTED criteria)[1] ($P = .958$). Higher RT doses were associated with increased OS independently of the volume of disease assessed at diagnosis or first referral ($P < .001$).

Table 3 Locoregional Treatment

	At Diagnosis (n = 18)	During Course of the Disease (n = 54)
TURP Only	13 (72.2%)	20 (37%)
Surgery Only	0	0
Radiotherapy Only	3 (16.7%)	28 (51.9%)
TURP and Surgery	0	1 (1.9%)
TURP and Radiotherapy	2 (11.1%)	5 (9.3%)
Radiotherapy and Surgery	0	0

Data are presented as n (%). Three patients had locoregional treatment at diagnosis and during the course of the disease: 2 patients had transurethral prostatectomy (TURP) at diagnosis and TURP during the course of the disease, and 1 patient had TURP at diagnosis and radiotherapy during the course of the disease.

Discussion

The past decade has seen a major change in therapeutic options for mPCa patients with several novel and effective drugs receiving regulatory approval, resulting in significant OS improvements. As a consequence, in our experience, an increasing number of patients are developing symptoms secondary to local progression of untreated primary disease. Furthermore, although the local tumor tends to respond well to initial ADT, the adaptive resistance mechanisms induced by subsequent lines of hormonal or chemotherapy treatment impair the chances of achieving adequate local control. Small increases in size of the local prostate tumor frequently result in urinary outflow obstruction and the invasion of adjacent organs that might manifest clinically with macroscopic hematuria, tenesmus, or hydronephrosis. In our study, more than a half of de novo mPCa patients had locally symptomatic disease at some point between diagnosis and death. The appropriate management of these local PCa complications remains challenging. Furthermore, therapeutic interventions might themselves be, in some cases, the cause of long-term side effects, such as erectile dysfunction, urinary incontinence, intestinal symptoms, and urinary tract infections.[19,20] In our study, a significant proportion of the patients who presented with local symptoms at diagnosis (18 of 44; 40.9%) reported persistent or worsening local symptoms despite local interventions. Nearly 1 in 5 M1 at diagnosis patients with local symptoms who did not receive definitive treatment to the primary tumor in the form of radical surgery or RT required multiple local interventions. This suggests that not treating the primary might not only have implications to patient morbidity and longevity but also health economics. However, RT treatment was efficacious in improving the local symptoms in only half of the treated patients, suggesting that this local intervention might have been administered too late in the disease course. The timing of administration of LRT should not necessarily coincide with the development of local symptoms but probably at the first evidence of radiological progression.

A recent study published in the *New England Journal of Medicine* analyzed patient-reported outcomes on the basis of questionnaires in patients with localized PCa treated with radical prostatectomy, RT, or active surveillance. Sexual dysfunction and urinary incontinence

Figure 1 (A) Locoregional Treatment (LRT) and Survival (Transurethral Prostatectomy [TURP] + Radiotherapy [RT]). (B) LRT and Survival (TURP Only). (C) LRT and Survival (RT Only)

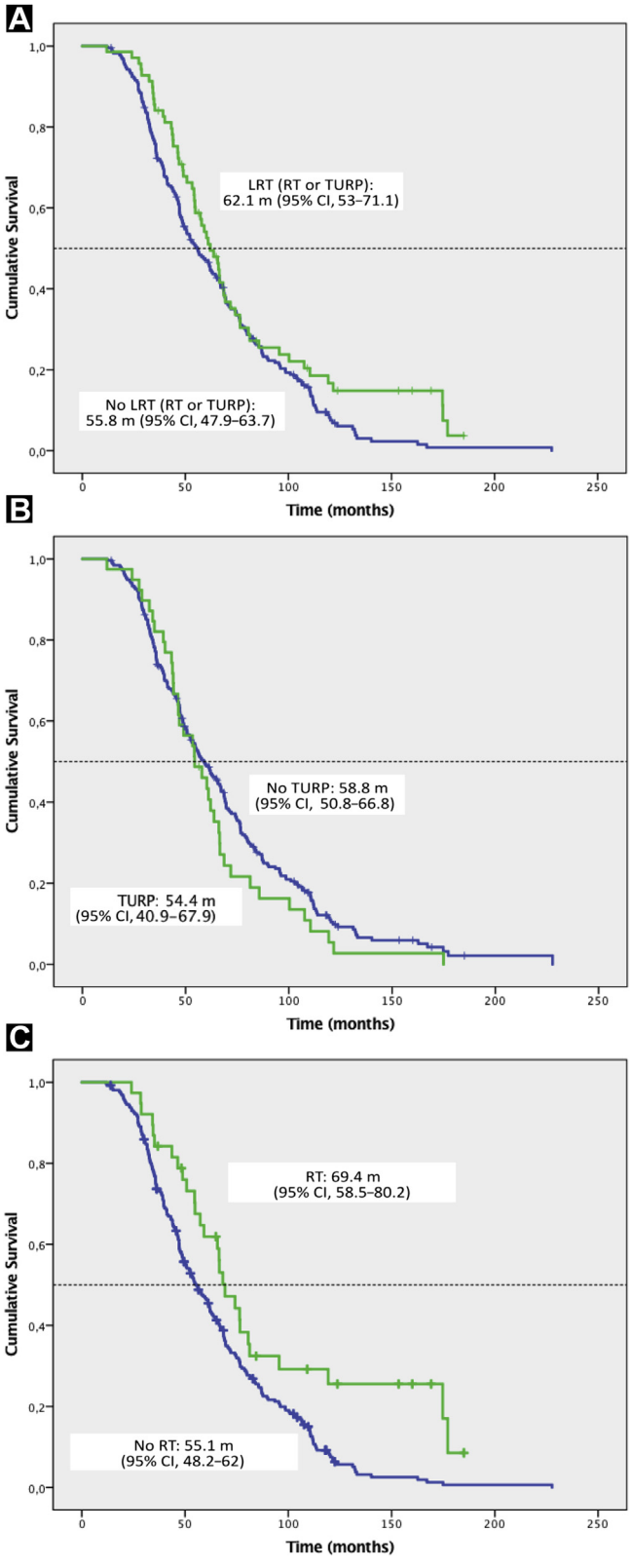

Table 4 Multivariable Survival Analysis

	HR (95% CI)	*P*
(A) LRT Including Radiotherapy as Well as TURP		
LRT	0.68 (0.48-0.96)	.030
Age	1 (0.98-1.02)	.766
PSA at Dx[a]	0.69 (0.55-0.86)	.001
Gleason score[b]	1.23 (0.93-1.76)	.132
Volume of metastases[c]	1.89 (1.39-2.58)	<.001
Symptoms at diagnosis	1.04 (0.97-1.11)	.303
(B) LRT When Only Radiotherapy is Considered		
LRT	0.53 (0.33-0.85)	.008
Age	1 (0.97-1.02)	.644
PSA at Dx[a]	0.7 (0.56-0.87)	.002
Gleason score[b]	1.29 (0.94-1.77)	.120
Volume of metastases[c]	1.8 (1.32-2.45)	<.001
Symptoms at diagnosis	1.03 (0.96-1.1)	.406

Abbreviations: CHAARTED = ChemoHormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease; Dx = diagnosis; HR = hazard ratio; LRT = locoregional treatment; PSA = prostate-specific antigen; TURP = transurethral prostatectomy.
[a]Prostate-specific antigen at diagnosis was log-transformed.
[b]Gleason score: ≥ 8 versus < 8.
[c]Volume of metastatic disease: high versus low as per CHAARTED criteria.

were the most frequently reported adverse events among patients treated with radical prostatectomy whereas RT more often induced changes in bowel habits especially in the long term.[21] The appropriate identification and timely management of patients with locally advanced disease who are most likely to develop clinically relevant local symptoms is therefore key to prevent patient morbidity.

This retrospective analysis suggests the possibility of an OS benefit from LRT in patients who present with mPCa at diagnosis. This hypothesis has already been proposed by other retrospective case series from different centers, with similar positive results.[4-8] Current guidelines for kidney, ovarian, and colorectal cancer recommend, whenever technically and clinically feasible, the surgical removal of the primary tumor and the metastatic sites.[9-13]

Here we explored the effect on OS of different local treatments analyzing RT and TURP as separate single interventions. As already mentioned, the primary tumor releases in the circulation tumor cytokines that might have a role in stimulating tumor growth at the metastatic sites.[15] This implies that any intervention to the local disease might favorably or unfavorably alter this mechanism and ultimately affect OS. We suggest the hypothesis that the administration of RT to the local tumor might improve OS through not only the suppression of the aforementioned paracrine cytokines but also the dissemination of tumor-derived neoantigens triggering an antitumoral immune response (abscopal effect). On the contrary, the effect of TURP is more unpredictable with mechanical trauma disrupting the anatomic barriers surrounding the tumor and favoring not only the circulation of tumor-derived cytokines and circulating tumor cells but also tumor neoantigens with consequent antitumor immune responses.[16,17] The effect of TURP on OS might therefore be different depending on which one of these two processes predominates. Nondefinitive LRT such as TURP might fail to fully abrogate the release of tumor-derived paracrine factors but still promote the intravascular dissemination of circulating tumor cells.[22] In fact, PCa cells can be detected in the circulation during the perioperative period in patients who undergo TURP and other studies have suggested an association of this procedure with disease progression.[22-24]

In our study, although local treatment (LRT) overall conferred a survival advantage (62.1 vs. 55.8 months; HR, 0.74; $P = .044$), this was almost entirely restricted to patients receiving RT (69.4 vs. 55.1 months; HR, 0.54; $P = .002$) as opposed to those who received TURP (54.3 vs. 58.8 months; HR, 1.23; $P = .239$). The survival benefit from local RT appeared to be independent of other known prognostic variables (age, Gleason Score, PSA, volume of disease, and presence of symptoms) included in multivariable Cox regression models. Importantly, the survival benefit was independent of the volume of bone metastases, suggesting that patients with a low as well as a high burden of metastases could potentially benefit from local RT. These results, although limited by the small number of patients and its retrospective nature, might indicate that the overall biological effect of TURP on OS is negligible whereas RT might instead have a favorable effect on OS. The different effect on OS between these 2 main local treatment modalities (RT or TURP) might be, in part, explained by the different rationale for treatment indication. Although TURP was generally carried out to resolve urinary symptoms such as urinary obstruction and/or urinary frequency, the rationale for administering RT in nearly half of the patients was primarily not to palliate local symptoms but rather to improve local control and prevent the subsequent development of local symptoms.

We acknowledge that our study has a number of limitations including its retrospective nature and our population heterogeneity. Relatively few patients received local treatment, which is consistent with current clinical practice, because local treatment in asymptomatic metastatic patients is not the current standard. With this, as with other similar retrospective studies published to date, treatment selection bias (ie, the selection of patients with better baseline prognostic features for local treatment at baseline) might significantly alter the interpretation of results. In our study, however, RT to the primary tumor was associated with significantly increased OS independently of other important baseline prognostic factors such as the volume of metastatic disease, Gleason score, or PSA level. Furthermore, the role of an "abscopal effect," suggested as a possible biological mechanism to support the role of LRT in advanced PCa, cannot be supported in our series because of the different timing of local therapy in our patients. The fact that not all patients had local treatment at baseline might have also led to the selection of those with favorable responses for local treatment along the course of the disease. Other studies supporting the role of local therapy in advanced PCa come from large databases that, unfortunately, do not contain most of the clinical parameters that were evaluated in our study. This is one of the first studies that takes into account the clinical heterogeneity of patients treated with local therapy, the very important methodological limitations to conducting similar analyses, therefore supporting the notion that well conducted, randomized prospective clinical trials are needed to correctly answer this very important clinical question.

Conclusion

Although this was a retrospective study limited by a risk of selection bias with the possibility of overestimating the OS effect of local radiation, these data support the rationale for conducting large randomized phase III trials to determine whether local treatment improves outcome for metastatic at diagnosis PCa patients. Moreover, our data make clear that not treating local disease in mPCa patients at diagnosis results in significant local disease morbidities during their lifetime with these patients commonly requiring invasive interventions with significant health economic implications particularly as patients with mPCa live longer with better systemic therapies.

Clinical Practice Points

- Local symptoms in de novo mPCa patients are common and often require multiple invasive interventions with significant effects in terms of morbidity and health economics.
- The definitive treatment of the primary tumor might favorably affect outcome and prevent local symptoms.
- Large randomized prospective clinical trials to investigate the OS benefit of RT to the primary tumor in de novo mPCa patients such as Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) are ongoing and results are eagerly awaited.

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