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European Association of Urology

Brief Correspondence

Identifying Optimal Candidates for Local Treatment of the Primary Tumor Among Patients Diagnosed with Metastatic Prostate Cancer: A SEER-based Study

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Article info

Article history:
Accepted August 21, 2014

Keywords:
Prostate cancer
Metastasis
Primary tumor treatment
Radical prostatectomy
Radiation therapy
Cancer-specific survival

Abstract

A recent study observed a survival benefit in men diagnosed with metastatic prostate cancer (mPCa) and managed with local treatment of the primary tumor (LT; either radical prostatectomy plus pelvic lymph node dissection or radiation therapy). We tested the hypothesis that only specific mPCa patients would benefit from LT and that the potential benefit would vary based on primary tumor characteristics. A total of 8197 mPCa patients at diagnosis (M1a, M1b, and M1c) were identified using the Surveillance Epidemiology and End Results database (2004–2011) and were divided according to treatment type: LT versus nonlocal treatment of the primary tumor (NLT; either androgen deprivation therapy or observation). Multivariable Cox regression analysis was used to predict cancer-specific mortality (CSM) in patients that received NLT. To assess whether the benefit of LT was different by baseline risk, we tested an interaction with CSM risk and LT. At multivariable analysis, all predictors were significantly associated with CSM, and the interaction test was statistically significant ($p < 0.0001$). Local treatment of the primary tumor, compared with NLT, conferred a higher CSM-free survival rate in patients with a predicted CSM risk <40%. The number needed to treat according to the predicted CSM risk at 3 yr after diagnosis remained substantially constant from 10% to 30%, whereas it exponentially increased for predicted CSM risk >40%. These results should serve as a foundation for future prospective trials.

Patient summary: Among metastatic prostate cancer patients, the potential benefit of local treatment to the primary tumor depends greatly on tumor characteristics, and patient selection is essential to avoid either over- or undertreatment.

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In patients with metastatic prostate cancer (mPCa) at diagnosis, treatment options are rather limited and life expectancy is greatly compromised. In these patients, local treatment of the primary tumor (LT) is not usually taken into account, whereas androgen deprivation therapy (ADT) represents the initial management of choice [1]. A recent, large, population-based study suggested that LT confers a survival benefit in mPCa patients [2]. This is in line with

http://dx.doi.org/10.1016/j.eururo.2014.08.056
0302-2838/

several studies focusing on other metastatic tumors [3,4], in which the reduction of primary tumor burden resulted in more favorable survival rates. Moreover, previous studies showed that the initial event at a metastatic site is not the arrival of tumor cells but rather the clustering of bone marrow–derived cells [5]. These cells make the local microenvironment of the secondary organ more receptive to tumor cell colonization and are stimulated by endocrine factors released by the primary tumor [6]. From this perspective, local treatment of the primary tumor could retard the formation and the growth of distant metastases; however, mPCa patients may represent a heterogeneous population, and the impact of LT on survival might be largely influenced by primary tumor characteristics. Given these premises, we aimed to test the impact of LT on cancer-specific mortality (CSM)–free survival.

We relied on the 2004–2011 Surveillance Epidemiology and End Results (SEER) database, which includes 18 registries. We included only patients with mPCa (M1a, M1b, or M1c) at diagnosis ($n = 19\ 337$). Excluded were patients with unknown prostate-specific antigen (PSA; $n = 2829$), T stage ($n = 4423$), or Gleason score ($n = 1947$). All patients were in the age range of 35–90 yr ($n = 144$ excluded). Patients were grouped according to treatment type: LT (either radical prostatectomy plus pelvic lymph node dissection or brachytherapy) versus nonlocal treatment of the primary tumor (NLT), defined as observation or ADT. Based on previously published methodology [2], patients treated with external-beam radiation therapy (EBRT) only ($n = 1797$) were excluded due to the lack of EBRT organ-site–specific codes within SEER. These selection criteria yielded 8197 evaluable patients.

Our statistical analyses consisted of three main steps. First, multivariable Cox regression analysis was used to predict CSM in patients that received NLT. Predictors consisted of age at diagnosis, PSA level, Gleason score (categorized as ≤6, 7, or ≥8), T stage (T2 or lower vs T3 or higher), N stage (N0/Nx vs N1), and M stage (categorized as M1a, M1b, or M1c). The discrimination of the model was corrected for overfit using 10-fold cross-validation. The predictive model was used to calculate the CSM risk at 3 yr after diagnosis for each patient. Second, we wished to assess whether the benefit of LT was different by baseline risk by testing an interaction with CSM risk and LT. We plotted the CSM-free survival rate at 3 yr against predicted CSM risk at 3 yr, according to treatment option (LT vs NLT). Third, we explored the variation of the number needed to treat (NNT) according to the predicted CSM risk at 3 yr after diagnosis.

A total of 8197 mPCa patients were included in this study (Table 1). Of these, 628 (8%) received LT, whereas 7569 (92%) underwent NLT. Median follow-up was significantly longer among survivors treated with LT compared with NLT (36 vs 31 mo, respectively; $p < 0.0001$). Supplementary Table 1 shows multivariable analysis predicting CSM in patients who received NLT. All predictors were significantly associated with CSM, whereas Harrell's C index was 0.61. The interaction test for the hypothesis that the impact of LT varies according to CSM risk was statistically significant ($p < 0.0001$). The CSM-free survival rate at 3 yr after diagnosis was plotted against the predicted CSM risk (the risk calculator and the formula to predict CSM risk at 3 yr are available at: http://www.urotecnologie.it/it/research), according to treatment option. Local treatment of the primary tumor, compared with NLT, conferred a higher CSM-free survival rate in patients with a predicted CSM risk <40% (Fig. 1). Conversely, when the predicted CSM risk exceeded 50%, LT did not provide a survival benefit. Finally, we evaluated variations of the NNT according to the predicted CSM risk at 3 yr after diagnosis (Supplementary Fig. 1). The NNT remained substantially constant from 10% to 30%, whereas it exponentially increased for predicted CSM risk >40%.

Our results confirmed our hypothesis and showed several important findings. First, our study is in line with the previous report by Culp et al. [2] that suggested a survival benefit of LT for the prostate in men diagnosed with mPCa; however, our observations are based on a larger and

Table 1 – Descriptive characteristics of 8197 patients diagnosed with metastatic prostate cancer between 2004 and 2011 within the Surveillance Epidemiology and End Results database, stratified according to treatment option

Variables	Local treatment ($n = 628$, 8%)	Nonlocal treatment ($n = 7569$, 92%)	p value
Age, yr, median (IQR)	65 (59–73)	71 (63–79)	<0.0001
Race, n (%)			0.7
White	466 (74)	5602 (74)	
Black	119 (19)	1445 (19)	
Other	41 (6.7)	423 (6)	
Unknown	2 (0.3)	99 (1)	
Marital status, n (%)			<0.0001
Married	431 (68)	4334 (57)	
Not married	171 (28)	2641 (35)	
Unknown	26 (4)	594 (8)	
PSA, ng/ml, median (IQR)	16 (7–54)	61 (20–98.0)	<0.0001
Gleason score, n (%)			<0.0001
≤6	70 (12)	380 (5)	
7	153 (24)	1562 (21)	
≥8	405 (64)	5627 (74)	
T stage, n (%)			<0.0001
T1	151 (24)	2306 (30)	
T2	220 (35)	3219 (43)	
T3a	66 (10)	580 (7)	
T3b	60 (10)	346 (5)	
T4	131 (21)	1118 (15)	
N stage, n (%)			0.7
N0	360 (57)	4318 (57)	
N1	143 (23)	1647 (22)	
Nx	125 (20)	1604 (21)	
M Stage			0.003
M1a	51 (8)	435 (5)	
M1b	432 (69)	5651 (75)	
M1c	145 (23)	1483 (20)	
Year of diagnosis, n (%)			0.9
2004	65 (10)	903 (12)	
2005	83 (13)	918 (12)	
2006	85 (13)	965 (13)	
2007	73 (12)	945 (13)	
2008	79 (13)	926 (12)	
2009	75 (12)	928 (12)	
2010	80 (13)	1000 (13)	
2011	88 (14)	984 (13)	

IQR = interquartile range; PSA = prostate-specific antigen.

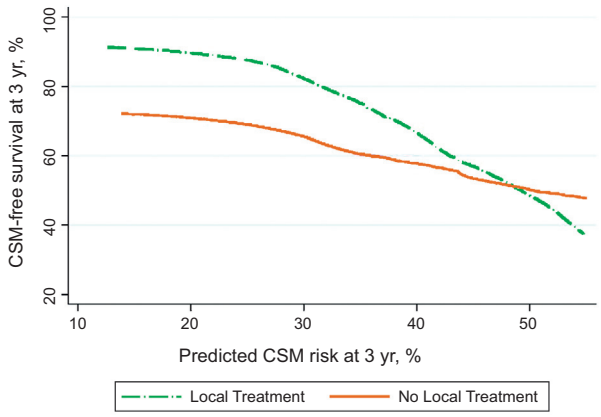

Fig. 1 – Cancer-specific mortality (CSM)–free survival rate plotted against predicted probability of CSM at 3 yr after diagnosis. Dashed green line indicates local treatment of the primary tumor. Solid orange line indicates no local treatment of the primary tumor.
CSM = cancer-specific mortality.

more contemporary cohort. Given the scarcity of treatment options for patients with mPCa and the very limited efficacy of these treatments, the survival benefit obtained by LT is considered very encouraging. Second, different from the aforementioned study, we aimed to identify optimal candidates for LT of the primary tumor. Accordingly, we developed a predictive model for mPCa patients based on tumor characteristics, and we evaluated the impact of LT on survival according to the predicted CSM risk. Interestingly, we found that LT conferred a survival benefit at 3 yr after diagnosis only in patients with a CSM risk $\leq$40%. Third, these results were confirmed when we evaluated the variations of the NNT according to the predicted CSM risk at 3 yr. Specifically, the NNT remained substantially constant from 10% to 30%, whereas it exponentially increased for predicted CSM risk $>$40%.

To the best of our knowledge, this study is the first to aim at identifying potential candidates for LT among patients with mPCa. Currently, in these patients, ADT is the standard of care, but patients invariably progress to castration-resistant disease [1], which represents the lethal form of the disease. Despite the introduction of novel agents [7,8], the prognosis of castration-resistant mPCa remains invariably poor [1]. From this perspective, our study may help improve cancer control in mPCa patients and serve as a foundation for future prospective trials. It is noteworthy that LT, in patients with predicted CSM risk $<$30%, was associated with a roughly 20% increase in survival at 3 yr, which is significantly higher than the survival benefit offered by any of the novel agents recently developed and approved to treat castration-resistant mPCa [7,8].

Our study is not devoid of limitations. First, the SEER database does not contain information on comorbidities that may represent a selection bias for treatment choice. Second, the SEER database does not provide information regarding disease extent and number of metastatic sites, which have been shown to be predictors of survival in previous reports [9]. These variables warrant investigation in future studies. Third, data regarding systemic therapies were also unavailable. The lack of information regarding hormonal therapies represents a major limitation of the current study. However, SEER is the only comprehensive population-based database in the United States and represents an ideal approach to study the survival of patients diagnosed with mPCa, especially in recent time periods [2]. Fourth, salvage treatment data were not available in the SEER database. However, it could be argued that salvage treatments for tumor progression could account just for a limited proportion of our findings. Fifth, median follow-up was significantly longer for survivors treated with LT compared with NLT. However, that difference consisted of few months (36 vs. 31 mo, respectively; $p < 0.0001$), and it is unlikely to modify our findings. Finally, the SEER database does not provide information regarding complications after treatment. Most probably, the complication rate in these patients is similar to what has been thoroughly reported in the literature regarding the complication rate of treating patients with locally advanced, nonmetastatic disease; however, this point warrants further investigation.

In conclusion, the potential and beneficial impact of local treatment of the primary tumor greatly depends on tumor characteristics, and patient selection is essential to avoid over- or undertreatment. If validated in future studies, our novel model can be of great help in selecting the optimal candidates for local treatment among mPCa patients.

Author contributions: Firas Abdollah had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fossati, Abdollah.
Acquisition of data: Fossati, Abdollah, Larcher.
Analysis and interpretation of data: Fossati, Abdollah, Trinh.
Drafting of the manuscript: Fossati, Abdollah, Trinh.
Critical revision of the manuscript for important intellectual content: Briganti, Sun, Karakiewicz, Sammon.
Statistical analysis: Fossati, Abdollah, Sood.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Guazzoni, Montorsi, Menon.
Other (specify): None.

Financial disclosures: Firas Abdollah certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.08.056. The risk calculator and the formula to predict CSM risk at 3 yr are available at http://www.urotecnologie.it/it/research.

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