



## Original Article

# Characteristics and national trends of patients receiving treatment of the primary tumor for metastatic prostate cancer<sup>☆</sup>

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## ABSTRACT

**Background:** We sought to determine temporal trends in the receipt of prostatectomy or locoregional radiation to the prostate for patients with metastatic prostate cancer and to identify predictors of receipt of local treatment.

**Methods:** We identified 39,976 patients with metastatic prostate cancer diagnosed in 2004–2012 using the National Cancer Database (NCDB). We used logistic multivariable regression to determine trends in the receipt of prostate and/or pelvic radiation or radical prostatectomy after adjusting for demographic and clinical factors.

**Results:** Patients with metastatic disease were less likely to receive locoregional treatment over time [7.88% in 2004 vs. 5.53% in 2012, adjusted odds ratio (AOR) = 0.97 per year, 95% confidence interval (CI) = 0.95–0.98;  $P < 0.001$ ]. Cofactors associated with decreased likelihood for locoregional treatment included older age (AOR = 0.96 per year, 95% CI = 0.96–0.96,  $P < 0.001$ ) and increased comorbidity level (1 comorbidity: AOR = 0.82, 95% CI = 0.73–0.93,  $P = 0.001$ ; two or more comorbidities: AOR = 0.49, 95% CI = 0.39–0.61,  $P < 0.001$ ). Decreasing utilization of both radiation and surgery of the primary site contributed to this trend. More specifically, patients with metastatic disease were less likely to receive radiation to the prostate and/or pelvis over time (5.9% in 2004 vs. 4.2% in 2012, AOR = 0.97 per year, 95% CI = 0.95–0.99,  $P < 0.001$ ). Similarly, there was a trend toward decreased use of radical prostatectomy (2.17% in 2004 compared to 1.31% in 2012, AOR = 0.96 per year, 95% CI 0.93–0.99,  $P = 0.01$ ).

**Conclusion:** Despite recent evidence of the possible benefit for locoregional treatment of prostate cancer in the setting of metastatic disease, rates of prostate radiation and radical prostatectomy among this population have actually declined over the 8-year period between 2004 and 2012, suggesting slow adoption of this novel treatment paradigm.

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## 1. Introduction

Prostate cancer remains the second most frequently diagnosed cancer in men and the leading cause of cancer death after lung cancer.<sup>1</sup> With the advent of improved awareness and screening programs, more cases are diagnosed at the early stages of prostate cancer. Still, <5% of patients will present with metastasis at diagnosis,<sup>2</sup> and up to 40% of patients will experience recurrence of

disease after conventional radical therapy.<sup>3</sup> Although the 5-year cause-specific survival rate for men who present without metastasis is nearly 100%, patients who present with metastasis have only 28% survival expectancy.<sup>4</sup> Appropriate treatment for this group of patients therefore remains an active area of interest.

Current guidelines recommend immediate or deferred hormone therapy [androgen deprivation therapy (ADT)] as palliative therapy for metastatic prostate cancer.<sup>5</sup> This treatment modality offers improvement of disease-related symptoms, delayed tumor progression, and increased survival.<sup>3</sup> Recent studies suggest that the use of local treatment of the primary tumor may improve outcomes for metastatic patients.<sup>6–11</sup> Similar work in breast cancer,<sup>12</sup> colon cancer,<sup>13</sup> and ovarian cancer<sup>14</sup> has suggested a survival benefit from local surgery or radiation.

<sup>☆</sup> Previous work: an abstract based on similar work was presented at the ASTRO 2016 meeting.

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Although data supporting local treatment of metastatic prostate cancer have accumulated in recent years, the retrospective nature of these studies has limited a more widespread adoption of the treatment paradigm. We sought to assess how trends in the treatment of metastatic prostate cancer have evolved in light of the shifting evidence for and against local treatment. Reflecting on current clinical practice patterns may inform future directions for study in these challenging patients.

## 2. Materials and methods

### 2.1. Data acquisition

Patient information was obtained from the National Cancer Database (NCDB) after approval from the Dana–Farber/Harvard Cancer Center Institutional Review Board. The NCDB is a national oncology database overseen by the Commission on Cancer and the American Cancer Society. Collectively, the database encompasses 70% of all newly diagnosed cases of cancer in the United States. For our purposes, patients with a diagnosis of prostate cancer were selected ( $n = 1,802,596$ ). We used a subset of patients with metastatic disease at the time of diagnosis based on the variable coded by the Collaborative Stage Data Collection System. The study was limited to patients diagnosed after 2004, when the variable was first introduced to the database ( $n = 39,976$ ). Patients for whom treatment data were unavailable were excluded.

### 2.2. Statistical analysis

Patient information was entered into STATA software (StataCorp LP, College Station, Texas, version 14.1) for data analysis. Demographic information was calculated according to coded variables in the NCDB database. Comparison of categorical variables was made using the chi-square test, whereas continuous variables were compared with Student *t* test. Logistic regression was performed in STATA for the treatment modalities of interest using year of diagnosis as a covariate and controlling for potential confounding factors such as age, race, income, education level, and comorbidity level (based on Charlson–Deyo Score). We used a two-sided *P* value of  $< 0.05$  as the criterion for statistical significance.

## 3. Results

### 3.1. Patient demographics

Based on review, 39,976 patients with metastatic prostate cancer diagnosed from 2004 to 2012 were identified. Patients were classified as those receiving definitive locoregional treatment (surgery or radiation of the primary tumor,  $n = 2,752$ ) or no locoregional treatment ( $n = 37,224$ ). From surgical cases, we did not count as definitive any patients who received only local destruction of tumor or local excision, or subtotal prostatectomy, or unspecified surgical procedures. Population characteristics are presented in Table 1 comparing no locoregional treatment to patients receiving locoregional treatment. Notable differences included increased age, higher rates of comorbidities, and higher rates of elevated prostate-specific antigen (PSA) among patients who did not receive locoregional therapy. Patients receiving locoregional therapy were more likely to have been treated at an academic institution.

### 3.2. Trends in time show decreasing utilization of locoregional treatment

Multivariable logistic regression showed that from 2004 to 2012, patients were less likely to receive locoregional treatment for

**Table 1**  
Patient demographics.

	No LTx ( $n = 37,224$ )	LTx ( $n = 2,752$ )	<i>P</i>
Median age (IQR)	72 (63–81)	66 (59–74)	0.0001
Race (%)			0.001
White	28,106 (75.5)	2,156 (78.3)	
African American	7,530 (20.2)	483 (17.6)	
Other	701 (1.9)	51 (1.9)	
Unknown	887 (2.4)	62 (2.3)	
Education level <sup>a)</sup>			<0.001
Bottom quartile	7,610 (20.4)	488 (17.7)	
Second quartile	8,583 (23.1)	616 (22.4)	
Third quartile	8,119 (21.8)	600 (21.8)	
Top quartile	11,348 (30.5)	945 (34.3)	
Unknown	1,564 (4.2)	103 (3.7)	
Income level <sup>b)</sup>			
Bottom quartile	6,345 (17.0)	393 (14.3)	
Second quartile	6,791 (18.2)	463 (16.8)	
Third quartile	10,032 (27.0)	730 (26.5)	
Top quartile	12,497 (33.6)	1,064 (38.7)	
Unknown	1,559 (4.2)	102 (3.7)	
Comorbidities (Charlson–Deyo Score)			<0.001
None	28,476 (76.5)	2,316 (84.2)	
One	5,973 (16.0)	346 (12.6)	
Two or more	2,775 (7.5)	90 (3.3)	
PSA, ng/mL (%)			<0.001
<10	3,942 (10.6)	876 (31.8)	
10–19	3,844 (10.3)	456 (16.6)	
20–30	2,355 (6.3)	200 (7.3)	
>30	26,535 (71.3)	1,181 (42.9)	
Unknown	548 (1.5)	39 (1.4)	
Treatment center type			<0.001
Nonacademic	24,603 (66.1)	1,688 (61.3)	
Academic	12,596 (33.8)	1,061 (38.6)	
Unknown	25 (0.1)	3 (0.1)	

IQR, interquartile range; LTx, locoregional treatment; PSA, prostate-specific antigen.

<sup>a)</sup> Education level is determined by proportion of residents in the patient's area code who have achieved a minimum high school degree with the bottom quartile ranking as areas with the lowest degree rates.

<sup>b)</sup> Income level is determined by average income of patients provided by zip code.

metastatic prostate cancer [7.88% in 2004 vs. 5.53% in 2012, adjusted odds ratio (AOR) = 0.97 per year, 95% confidence interval (CI) = 0.95–0.98,  $P < 0.001$ ] (Fig. 1). Cofactors associated with decreased likelihood for locoregional treatment included older age (AOR = 0.96, 95% CI = 0.96–0.96,  $P < 0.001$ ) and increased comorbidity level (1 comorbidity: AOR = 0.82, 95% CI = 0.73–0.93,  $P = 0.001$ ; 2 or more comorbidities: AOR = 0.49, 95% CI = 0.39–0.61,  $P < 0.001$ ). Patients in the top income quartile assessed by zip code were found to be more likely to receive locoregional treatment (AOR = 1.25 per year, 95% CI = 1.06–1.48,  $P = 0.007$ ). Race, education, and income level did not otherwise predict receipt of locoregional treatment (Table 2).

### 3.3. Trends in locoregional therapy are contributed to by decreased use of both radiation and surgery

Trends in utilization of locoregional therapy were subdivided into treatment with radiation to the prostate and/or pelvis or surgery of the primary site for further analysis. Radiation therapy included the use of external beam and brachytherapy or combined modality treatment. Multivariable logistic regression again showed that patients were less likely to receive locoregional radiation (5.9% in 2004 to 4.2% in 2012, AOR = 0.97 per year, 95% CI = 0.95–0.99,  $P < 0.001$ ) (Table 3). Treatment with radiation was also stratified by PSA (recorded as the highest PSA documented prior to diagnostic biopsy) to see if trends were different in patients with low PSA as a

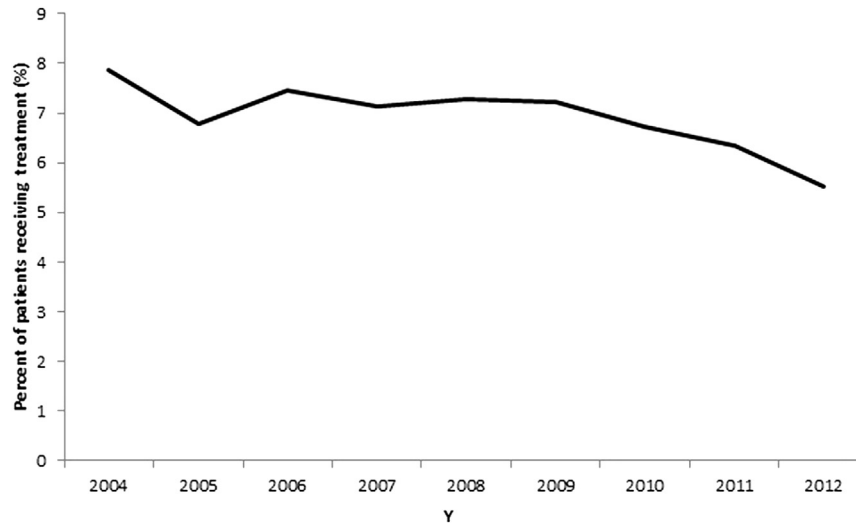


Fig. 1. Trends in locoregional therapy during study period of 2004–2012.

Table 2

Multivariate logistic regression of changes in locoregional therapy usage over time stratified by covariates.

Covariate	AOR	95% CI	P
Age	0.96	0.96–0.96	<0.001
Race			
White	1.13	0.86–1.48	0.376
Black	0.87	0.65–1.15	0.321
Education level			
Bottom quartile	Ref		
Second quartile	1.06	0.92–1.21	0.425
Third quartile	1.06	0.91–1.23	0.431
Top quartile	1.16	0.99–1.36	0.073
Income level			
Bottom quartile	Ref		
Second quartile	1.06	0.91–1.23	0.454
Third quartile	1.11	0.95–1.29	0.178
Top quartile	1.25	1.06–1.48	0.007
Comorbidities (Charlson–Deyo Score)			
None	Ref		
One	0.82	0.73–0.93	0.001
Two or more	0.49	0.39–0.61	<0.001

AOR, adjusted odds ratio; CI, confidence interval.

Table 3

Adjusted odds ratio of changes in treatment modalities over time.

Treatment type	AOR	95% CI	P
Locoregional	0.97	0.95–0.98	<0.001
M1a	0.97	0.93–1.01	0.15
M1b	0.96	0.94–0.98	<0.001
M1c	0.97	0.93–1.00	0.071
Radiation	0.97	0.95–0.99	<0.001
M1a	0.98	0.93–1.03	0.366
M1b	0.96	0.94–0.99	0.001
M1c	0.96	0.92–1.00	0.061
Surgery	0.96	0.93–0.99	0.01
M1a	0.95	0.88–1.02	0.18
M1b	0.97	0.93–1.01	0.125
M1c	0.99	0.92–1.06	0.725
Chemotherapy	0.99	0.97–1.00	0.131
M1a	0.99	0.94–1.05	0.819
M1b	0.99	0.97–1.01	0.373
M1c	1.02	0.99–1.05	0.239
ADT	1.05	1.04–1.06	<0.001
M1a	1.04	1.00–1.08	0.044
M1b	1.04	1.03–1.06	<0.001
M1c	1.03	1.01–1.05	0.007

ADT, androgen deprivation therapy; AOR, adjusted odds ratio; CI, confidence interval; M1a, metastasis to distant lymph nodes; M1b, metastasis in bones ± distant lymph nodes; M1c, metastasis other than distant lymph nodes or bones.

proxy for low-volume disease. However, logistic regression did not show any significant interaction between year of diagnosis and PSA < 10.0 ng/mL ( $P_{\text{interaction}} = 0.120$ ). Finally, subgroup analysis was performed for academic versus nonacademic centers. There was no significant difference in the trends among patients treated at academic versus nonacademic centers ( $P_{\text{interaction}} = 0.839$ ), as the use of radiation decreased at both academic (6.5% in 2004 to 4.2% in 2012) and nonacademic (5.6% in 2004 to 4.2% in 2012) institutions. Similarly, there was a trend toward decreased use of surgery of the primary site for patients presenting with metastatic disease (2.17% in 2004 compared to 1.31% in 2012, AOR = 0.96 per year, 95% CI 0.93–0.99,  $P = 0.01$ ) (Fig. 2).

Finally, subgroup analysis of locoregional trends was performed by stratifying over M stage. There was a decrease in the use of locoregional treatment for M1b patients (metastasis in bone ± distant lymph nodes), but the trend was not significant for M1a (distant lymph nodes) or M1c (other distant metastasis ± bone or distant lymph nodes). In looking specifically at patients receiving radiation, there was again a decrease in treatment for M1b patients but not for M1a or M1c patients. No significant trends were found among patients undergoing surgery (Table 3).

### 3.4. Trends in use of systemic therapies differ over time

Use of systemic therapy including ADT and chemotherapy was trended over time. Overall, there was no change in the use of chemotherapy in newly diagnosed metastatic patients (AOR = 0.99, 95% CI 0.97–1.00,  $P = 0.13$ ). By comparison, use of ADT in patients with metastatic prostate cancer was higher than use of any locoregional therapy. Logistic regression for use of ADT showed a significant increase over time (70.2% in 2004 compared to 77.9% in 2012, AOR = 1.05 per year, 95% CI 1.04–1.06) (Fig. 2). Stratification of systemic therapy by M stage (as above) showed a nonsignificant increase in use of chemotherapy for M1c patients despite an overall decrease chemotherapy use and decreases in the M1a and M1b subgroups. The increase in use of ADT was composed of increases in treatment in all subgroups (M1a–M1c) (Table 3).

## 4. Discussion

The objective of this study was to quantify changes in the use of locoregional treatment for metastatic prostate cancer over time. We found that the rate of locoregional treatment (radiation or

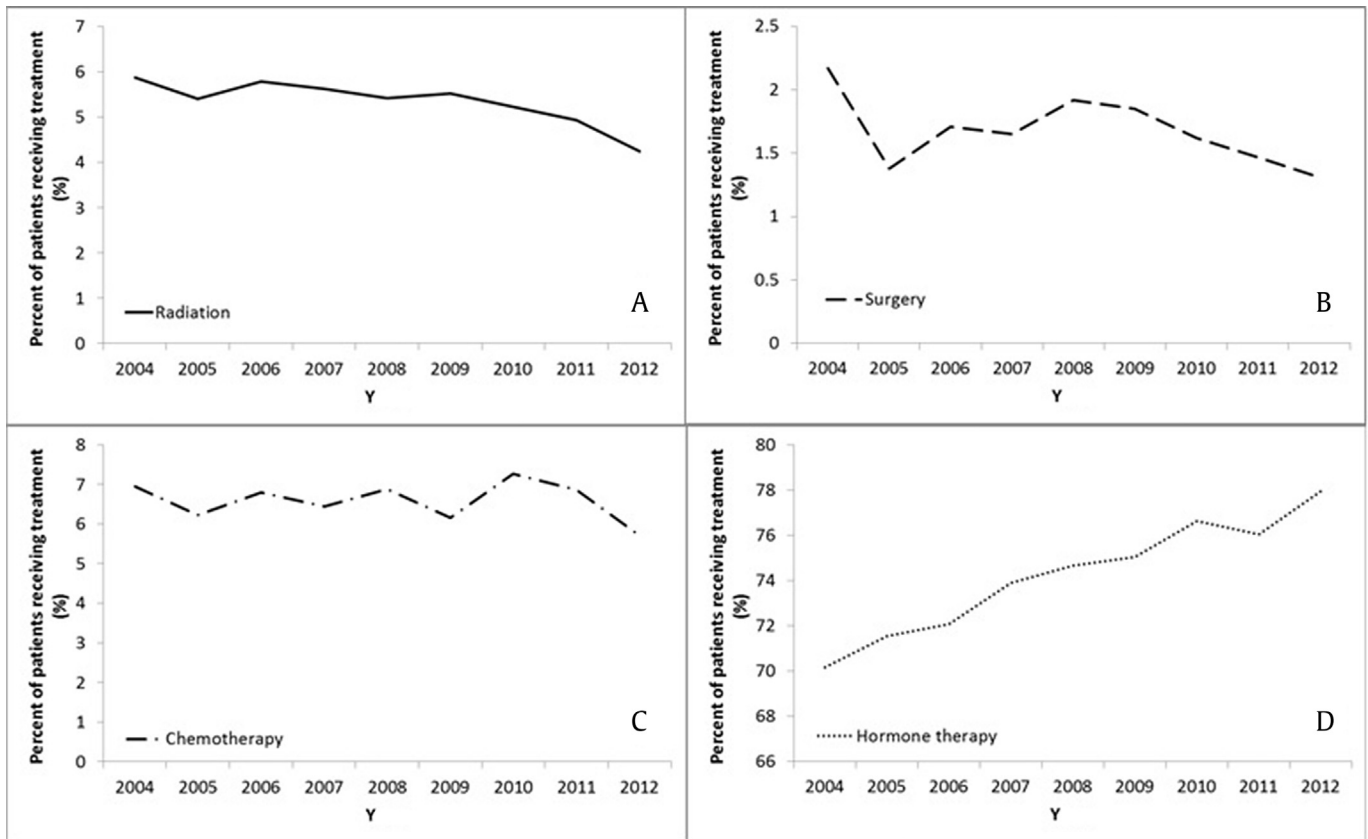


Fig. 2. Trends in treatments for metastatic prostate cancer show decreasing trends in locoregional treatment (A) radiation and (C) surgery, whereas systemic therapy shows no significant trends in (C) chemotherapy and increasing trend in (D) hormone therapy.

surgery) given to the prostate decreased during our study period (from 7.88% to 5.53% between 2004 and 2012), and that older age and increased comorbidity on the Charlson–Deyo score were predictors of decreased treatment. More specifically, subdivision of locoregional treatment showed that the decreasing trend was composed of decreases in both local radiation and surgery of the primary site. Stratification by M stage showed a decrease in treatment of M1b patients with locoregional therapies and a similar decrease in use of radiation for M1b patients. Changes in treatment of M1a and M1c patients along with use of surgery for oligometastatic patients were not significant. Conversely, there was an increasing trend in the use of ADT for newly diagnosed metastatic patients.

This result was surprising because of the emerging data on the potential value of locoregional treatment in node positive and metastatic disease.<sup>6–11</sup> For example, in a review of the SEER (Surveillance, Epidemiology, and End Results)-Medicare database, Satkunasingam et al<sup>15</sup> showed that radical prostatectomy and intensity-modulated radiation therapy (IMRT) were associated with decreased risk of prostate cancer-specific mortality at 6 months (52% reduction and 62% reduction, respectively) relative to no local therapy for patients with metastatic prostate cancer. Additionally, Culp et al<sup>3</sup> showed that 5-year survival and disease-specific survival were significantly higher after radical prostatectomy (67.4% and 75.8%, respectively) or brachytherapy (52.6% and 61.3%, respectively) compared to no local treatment (22.5% and 48.7%, respectively) among men with Stage IV disease.<sup>3</sup> Most recently, Loppenberg et al<sup>16</sup> used NCDB data to demonstrate improved 3-year overall mortality-free survival rates in metastatic prostate cancer patients who were treated with local therapy compared to

no local therapy (66% vs. 51%, respectively;  $P < 0.001$ ). Parikh et al<sup>17</sup> found that among NCDB patients, 5-year overall survival was improved for patients who received local therapy compared to those who did not (45.7% vs. 17.1%,  $P < 0.01$ ), although only radical prostatectomy and IMRT—but not 2D/3D conformal radiation therapy—conferred overall survival benefit compared to no local therapy. Notably, this study excluded patients who received chemotherapy who were included here to inform comparisons between local and systemic therapy use.<sup>17</sup> Similarly, Rusthoven et al<sup>18</sup> found that among metastatic prostate cancer patients treated with ADT, addition of prostate radiotherapy (RT) improved overall survival on univariate ( $P < 0.001$ ) and multivariate analysis (hazard ratio = 0.624, 95% CI = 0.551–0.706,  $P < 0.001$ ) adjusted for age, year, race, comorbidity score, PSA level, Gleason score, T stage, N stage, chemotherapy administration, treating facility, and insurance status. Despite differences in inclusion criteria (notably, exclusion of chemotherapy patients in Parikh et al's study<sup>17</sup> and limitation to ADT patients in Rusthoven et al's study<sup>18</sup>), our paper aligns well with these NCDB studies in showing the decreasing trend in use of local therapy despite the apparent benefit. Kaplan et al<sup>19</sup> discuss that treatment of the primary site may be of importance in preventing further metastatic spread because of factors secreted, in addition to oncogenic cells, that promote growth in secondary sites. A supporting study showed that circulating malignant cells had decreased metastatic potential after treatment of the primary tumor.<sup>20</sup> Specifically, in renal cell carcinoma, two randomized trials comparing treatment of patients presenting with metastatic cancer found that systemic therapy combined with radical nephrectomy showed significant survival benefit.<sup>21,22</sup> These findings lend legitimacy to the theory that

locoregional treatment of the primary tumor may improve outcomes for metastatic prostate cancer.

One possible explanation for the decreasing trend is that the studies focusing exclusively on local therapy for metastatic disease were published in recent years, and so there was no time for these data to be reflected in practice patterns prior to 2012.<sup>3,4,15,16</sup> However, it should be noted that there was some evidence suggesting the value of definitive local therapy for node-positive disease prior to 2012, and it is therefore still somewhat surprising that local therapy continued in a downward trajectory from 2004 to 2012 rather than slightly increasing or being stable.<sup>7</sup> Nevertheless, in the absence of prospective, randomized data evaluating the use of local therapy for metastatic disease, practice patterns have relied heavily on previous recommendations. Several ongoing trials will inform future changes in practice patterns. Notably, the STAMPEDE trial (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy, NCT00268476) and the HORRAD trial (ISRCTN 06890529) will compare ADT alone to ADT with radiation. PEACE1 (NCT01957436) will compare ADT ± RT ± abiraterone acetate with prednisone ± docetaxel. Finally, study NCT01751438 will compare systemic therapy combined with radiation or surgery to systemic therapy alone. Changes in practice patterns in light of these ongoing results ought to be compared to previous practice patterns to better understand the changes in outcomes for patients with metastatic prostate cancer.

Another possible explanation is that the years 2004 to 2012 were particularly exciting in terms of the development of new systemic therapies for metastatic prostate cancer. Starting with survival improvements from docetaxel in 2004 to the advent of abiraterone, enzalutamide, sipuleucel-T, cabazitaxel, and radium-223 after 2008, the large number of new systemic therapies for metastatic disease may have led physicians to use local therapy less for metastatic disease. However, as none of these therapies is permanently curative and as there is emerging retrospective data on the potential value of definitive therapy in metastatic disease, we may start to see this trend abate in future studies after 2012. Additional randomized controlled trials may elucidate the utility of radiation and surgery of the primary site. Accordingly, an additional arm was added to the STAMPEDE trial, which will investigate the role of RT in metastatic disease.<sup>23</sup>

Originally published in 1996, the National Comprehensive Cancer Network guidelines recommend ADT as the primary treatment modality for metastatic prostate cancer. Oligometastatic disease, in particular, is treated with ADT alone per guidelines. Our findings suggest that conformation to the National Comprehensive Cancer Network guidelines was increasing in both academic and nonacademic settings over this period, as the use of ADT for metastatic disease increased from 70.2% in 2004 compared to 77.9% in 2012.

In light of these emerging data, the decreasing trend in use of locoregional treatment may change. The practice patterns illustrated in 2004–2012 may be contrasted to future trends as the paradigm shifts. Changes in the outcomes of patients with metastatic disease ought to be interpreted in light of the evolving practice patterns illustrated here (Table 3). In addition, as the frequency of screening for prostate cancer changes, more patients may present with advanced disease. Understanding the treatment of these complex patients will become increasingly important.

This study has certain limitations. As discussed, because our dataset was limited to patients diagnosed between 2004 and 2012, more recent trends could not be observed. In addition, owing to the retrospective nature of the study, confounding factors may exist that were not accounted for. Importantly, because detailed data regarding metastatic number and sites for patients were not available, this information could not be factored into treatment

consideration. Finally, because of the data available in the NCDB, we were unable to differentiate between trends in treatment for oligometastatic versus widely metastatic disease. We attempted to address this limitation using subgroup analysis based on PSA score, but no differences were found.

## 5. Conclusion

The use of definitive local treatment for metastatic prostate cancer decreased from 2004 to 2012, possibly because of advances in systemic therapy during this time. Given the recent accumulating evidence on the value of local therapy in improving outcomes for these patients, these trends may reverse in the future; however, prospective randomized trials are needed to clarify the exact benefit.

## Conflicts of interest

P.L.N. is a consultant for Medivation/Astellas and Genome DX. F.Y.F. has consulted for Medivation/Astellas, Celgene, and Genome Dx. The other authors have nothing to disclose.

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## References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;(64):9–29.
2. Ryan CJ, Elkin EP, Small EJ, Duchane J, Carroll P. Reduced incidence of bony metastasis at initial prostate cancer diagnosis: data from CaPSURE. *Urol Oncol* 2006;24:396–402.
3. Culp SH, Schellhammer PF, Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. *Eur Urol* 2014;65:1058–66.
4. Aoun F, Peltier A, van Velthoven R. A comprehensive review of contemporary role of local treatment of the primary tumor and/or the metastases in metastatic prostate cancer. *Biomed Res Int* 2014;2014:501213.
5. Scardino P. Update: NCCN prostate cancer clinical practice guidelines. *J Natl Compr Canc Netw* 2005;3:S29–33.
6. Mottet N, Peneau M, Mazon JJ, Molinie V, Richaud P. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. *Eur Urol* 2012;62:213–9.
7. Verhagen PC, Schroder FH, Collette L, Bangma CH. Does local treatment of the prostate in advanced and/or lymph node metastatic disease improve efficacy of androgen-deprivation therapy? A systematic review. *Eur Urol* 2010;58:261–9.
8. Morgan PB, Hanlon AL, Horwitz EM, Buyyounouski MK, Uzzo RG, Pollack A. Radiation dose and late failures in prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;67:1074–81.
9. Engel J, Bastian PJ, Baur H, Beer V, Chaussy C, Gschwend JE, et al. Survival benefit of radical prostatectomy in lymph node-positive patients with prostate cancer. *Eur Urol* 2010;57:754–61.
10. Ghavamian R, Bergstralh EJ, Blute ML, Slezak J, Zincke H. Radical retropubic prostatectomy plus orchiectomy versus orchiectomy alone for pT<sub>x</sub>N<sub>+</sub> prostate cancer: a matched comparison. *J Urol* 1999;161:1223–7. discussion 1227–8.
11. Steuber T, Budaus L, Walz J, Zorn KC, Schlotmann T, Chun F, et al. Radical prostatectomy improves progression-free and cancer-specific survival in men with lymph node positive prostate cancer in the prostate-specific antigen era: a confirmatory study. *BJU Int* 2011;107:1755–61.
12. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998;352:930–42.

13. Glehen O, Mohamed F, Gilly FN. Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia. *Lancet Oncol* 2004;5:219–28.
14. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;20:1248–59.
15. Satkunasivam R, Kim AE, Desai M, Nguyen MM, Quinn DI, Ballas L, et al. Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: a SEER-Medicare analysis. *J Urol* 2015;194:378–85.
16. Loppenberg B, Dalela D, Karabon P, Sood A, Sammon JD, Meyer CP, et al. The impact of local treatment on overall survival in patients with metastatic prostate cancer on diagnosis: a National Cancer Data Base analysis. *Eur Urol* 2017;72:14–9.
17. Parikh RR, Byun J, Goyal S, Kim IY. Local therapy improves overall survival in patients with newly diagnosed metastatic prostate cancer. *Prostate* 2017;77:559–72.
18. Rusthoven CG, Jones BL, Flaig TW, Crawford ED, Koshy M, Sher DJ, et al. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. *J Clin Oncol* 2016;34:2835–42.
19. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature* 2005;438:820–7.
20. Psaila B, Lyden D. The metastatic niche: adapting the foreign soil. *Nat Rev Cancer* 2009;9:285–93.
21. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;345:1655–9.
22. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;358:966–70.
23. Parker CC, Sydes MR, Mason MD, Clarke NW, Aebbersold D, de Bono JS, et al. Prostate radiotherapy for men with metastatic disease: a new comparison in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial. *BJU Int* 2013;111:697–9.