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Definitive and sustained increase in prostate cancer metastases in the United States

Neal A. Patel, M.D.[a], Art Sedrakyan, M.D. Ph.D.[b], Fernando Bianco, M.D.[c], Ruth Etzioni, Ph.D.[d], Michael A. Gorin, M.D.[e], Wei-Chun Hsu, M.S.[b], Jialin Mao, M.D. M.S.[b], Paul L. Nguyen, M.D.[f], Edward Schaeffer, M.D. Ph.D.[g], Jonathan Shoag, M.D.[a], Andrew Vickers, Ph.D.[h], Jim C. Hu, M.D. M.P.H.[a,*]

[a] *Department of Urology, Weill Cornell Medicine-New York Presbyterian Hospital, New York, NY*
[b] *Department of Healthcare Policy and Research, Weill Cornell Medicine, New York, NY*
[c] *Nova Southeastern University, Fort Lauderdale, FL*
[d] *Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA*
[e] *Department of Urology, Johns Hopkins University School of Medicine, Baltimore, MD*
[f] *Department of Radiation Oncology, Dana Farber Cancer Institute, Boston, MA*
[g] *Department of Urology, Feinberg School of Medicine, Northwestern University, Chicago, IL*
[h] *Department of Epidemiology, Memorial Sloan-Kettering Cancer Center, New York, NY*

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Abstract

Introduction: We examined the most recent Surveillance, Epidemiology, and End Results release to corroborate temporal trends in nonmetastatic and distant prostate cancer metastases in the United States.

Methods: Surveillance, Epidemiology, and End Results was analyzed for the incidence of nonmetastatic and distant metastasis for men with prostate cancer aged 50–74 and ≥75 years during 2004–2015. Incidence ratios (IR) were calculated relative to the year prior.

Results: The incidence of distant metastasis significantly increased from 451.0 to 504.0 per million (IR:1.12, 95% CI:1.01–1.24) from 2011 to 2012 and 532.3 to 586.1 per million (IR:1.10, 95% CI:1.00–1.21) from 2014 to 2015 in men aged ≥75 years. The incidence of distant metastasis did not significantly increase in men aged 55–74 over the study period.

Conclusion: We demonstrate a sustained and definitive increase in prostate cancer distant metastases in men aged ≥75 years. Although our observational study design cannot pinpoint the exact cause of this increase, which is likely multifactorial, this shift reverses declines in metastases at diagnoses that followed the advent of prostate-specific antigen screening.

1. Introduction

Due to the high incidence of prostate cancer in men and the potential to cure localized disease, population screening programs were implemented in the United States in the 1990s [1]. With the introduction of widespread prostate-specific antigen screening, a significant decrease in the incidence of metastatic disease at presentation and more importantly a decline in prostate cancer specific (PCSM) mortality was observed [2].

Following consecutive years of decline a significant increase in distant prostate cancer metastases at diagnosis was witnessed from 2011 to 2013 in the United States [3]. However, these findings were met with justifiable skepticism due to concerns that the rise, following a decline from 2004 to 2011, may be due to random statistical variation [4]. In this study, using the most recent Surveillance, Epidemiology, and End Results (SEER) release, we sought to further examine the temporal trends in nonmetastatic and distant metastases.

2. Methods

We analyzed SEER Collaborative Staging for the incidence per million US men, standardized to the population

*Corresponding author. Tel: (646) 962-9600, fax: (646) 962-0715.
E-mail address: jch9011@med.cornell.edu (J.C. Hu).

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in 2000, of nonmetastatic disease (T1-T4N0M0) and distant metastasis (M1) for men aged 50–74 and ≥75 years during 2004–2015. T-stage was determined clinically and N and M stage were based on combined information from clinical and pathological assessment, as determined by SEER. To account for missing stage, incidence rates were derived by applying the proportion of each disease stage to the total number of men diagnosed with prostate cancer [3]. Temporal trends in incidence were visualized with restricted cubic spline or linear model by quarter. Incidence ratios (IR) with 95% confidence intervals (CI) were calculated relative to consecutive years (e.g., 2015 vs. 2014) as done in prior temporal analysis studies [5,6]. All analyses were performed using SAS v9.3 (SAS Institute, Cary, NC).

3. Results

The incidence of nonmetastatic prostate cancer decreased from 4618.0 to 2977.7 per million in men aged 50–74 years and from 6919.3 to 3221.1 per million in men aged ≥75 years between 2004 and 2015 (Fig. 1). On the other hand, the incidence of distant metastases gradually increased from 130.1 to 157.3 per million men aged 50–74 years between 2007 and 2015 after the slight decline between 2005 and 2007; and from 451.0 to 586.1 per million men aged ≥75 years between 2011 and 2015 after the progressive decline between 2004 and 2011. Notably, the incidence of distant metastasis significantly increased from 451.0 to 504.0 per million (IR: 1.12, 95% CI: 1.01–1.24) from 2011 to 2012 and 532.3 to 586.1 per million (IR: 1.10, 95% CI: 1.00–1.21) from 2014 to 2015 in men aged ≥75 years.

4. Discussion

Using recent evidence from a national tumor registry and methodology consistent with prior studies [5,6], we demonstrate a definitive increase in distant metastases in men aged 75 years and older in 2015 that contrasts a relatively stable incidence between 2005 and 2011. These findings coincide with an overall decrease in the incidence of prostate cancer, which may be either secondary to a decline in prostate-specific antigen screening, or a depletion in prevalence due to widespread dissemination of prostate biopsies and treatment in the early 2000s. However, the increased incidence of distant metastases in elderly men from 2011 to 2013 in our prior study [3] that is sustained in 2015 is concerning. The morbidity and detriment to quality of life that is associated with hormonal therapy and chemotherapy, the standard of care in men distant metastases, is significant and confers a higher risk for PCSM [7].

Our use of SEER Collaborative Staging differs from earlier studies [5,6]. Collaborative Staging better represents prostate cancer staging compared to SEER Summary Staging in which localized and regional stages are pooled into a

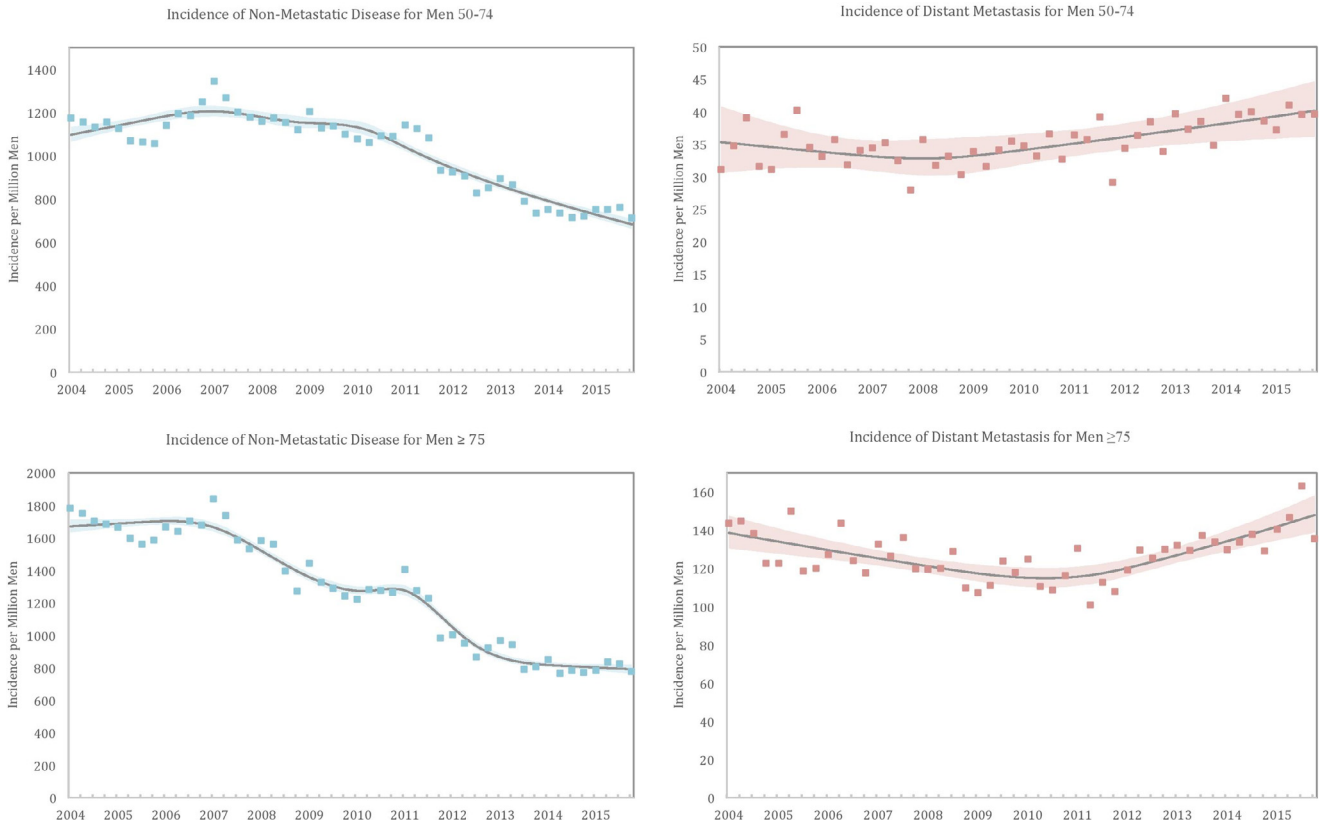

Fig. 1. Standardized prostate cancer incidence of nonmetastatic and distant metastases by quarter during 2004–2015.

"loco-regional" categorization. This clustering of nodal disease is difficult to interpret as regional disease in Summary staging is comprised of pT3, pT4, and N1, despite these disease states having distinctly different prognosis and clinical management. Our use of Collaborative Staging, a more contemporary classification scheme is more clinically relevant as it separates out pelvic lymph node metastases. Men with isolated pelvic lymph nodes metastases clearly have a worse overall survival even when treated with aggressive multimodal treatments and thus should not be pooled with localized disease [8].

The observed rise in distant metastases in older men could be for several reasons. First, the absence of an increase in men younger than 75 years may be due to the United States Preventive Services Task Force's (USPSTF) recommendation in 2008 against prostate cancer screening in men 75 years or older. However, given the significant lead time associated with prostate cancer progression it is unclear how much time is required to elapse before epidemiologic shifts manifest. Second, the median age of death from prostate cancer is 80 years old [9]. Thus, metastases are likely to be seen in older men compared to younger men who are often diagnosed in the window of curability.

The rise in distant metastases should also be interpreted with caution given the changing landscape of imaging used for prostate cancer staging. However, attributing the increases in the incidence of metastases at diagnosis to advances in imaging may not currently be a well-supported hypothesis for several reasons. First, the standard imaging modality for distant metastases during our study period has remained bone scan [10]. New technologies such as Choline positron emission tomography (PET) and PET/CT are still experimental and not widely utilized in the United States [11,12]. Also during the study period, prostate specific membrane antigen PET was not and is still not approved by the Food and Drug Administration (FDA). Second, although there has been an increase in the use of multiparametric magnetic resonance imaging, this modality is not typically used to assess distant disease. Additionally, magnetic resonance imaging, even with diffusion weighted imaging has not increased in sensitivity to detect clinical metastases, which are still radiographically positive at greater than 1 cm [12–14].

In conclusion, we demonstrate significant epidemiologic shifts in disease presentation that has significant implications for prostate cancer screening guidelines and management of disease burden at diagnoses. The recent shift USPSTF shift toward individualized screening for men aged 55–69 years along with the strong uptake of active surveillance [15] may attenuate over-detection and overtreatment of indolent disease while capturing clinically significant prostate cancer within the window of curability. Continued, close monitoring of population-based shifts in disease presentation is needed to determine the downstream epidemiologic sequelae on PCSM.

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