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Original Article

Who Dies From Prostate Cancer? An Analysis of the Surveillance, Epidemiology and End Results Database☆

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Abstract

Aims: To characterise the presenting features of those who ultimately die from prostate cancer (PCa).
Materials and methods: The study population consisted of patients in the Surveillance, Epidemiology and End Results (SEER) Program database diagnosed with PCa between 1990 and 2015. Patients were assigned to the following clinical risk groups: low-risk localised (LRL), intermediate-risk localised (IRL), high-risk localised (HRL), node-positive and metastatic (M1). Before 2004, in the absence of prostate-specific antigen (PSA) and Gleason score data, patients with cT1-T2aN0M0 and low-grade PCa were classified as LRL, those with cT3-4N0M0 or high-grade PCa were classified as HRL and all others with N0M0 disease were classified as IRL. The primary aim was to describe the risk group distribution of those who ultimately died from PCa compared with those who were diagnosed with PCa over the study period. A secondary aim was to estimate PCa-specific survival (PCSS) and evaluate the association of risk group with PCSS.
Results: Among a total of 811 487 patients who were diagnosed with PCa, data sufficient for risk group determination were present in 635 733 patients. The median follow-up was 83 months. The overall risk group distribution at diagnosis was as follows: LRL 10.5%, IRL 49.7%, HRL 34.8%, node-positive 1.5% and M1 3.5%. The risk group distribution of those who died from PCa was 3.9%, 29.4%, 40.9%, 3.2% and 22.8%, respectively. Compared with LRL PCa, the adjusted hazard ratio (95% confidence interval) for PCSS was 1.40 (1.33–1.46) in IRL, 3.76 (3.60–3.93) in HRL, 11.87 (11.14–12.65) in node-positive and 37.12 (35.43–38.88) in M1.
Conclusions: In this large contemporary cohort, patients with M1, node-positive and HRL disease accounted for two-thirds of all deaths from PCa. *De novo* metastatic PCa was associated with an approximately 40-fold increased risk of death from PCa compared with LRL PCa. Efforts to improve PCSS will therefore depend largely on improvements in therapy in those with M1, node-positive and HRL disease.

Key words: Epidemiology and End Results; Prostate cancer; prostate cancer mortality; risk stratification; Surveillance

Introduction

Prostate cancer (PCa) is the second most common cancer in men worldwide, accounting for 15% of all cancer diagnoses globally in men [1]. Despite a substantial rise in the incidence of PCa over time, the overall PCa-specific survival (PCSS) has been relatively constant and there is no significant global variation in death from PCa [2]. In a UK registry study of about 50 000 PCa patients, Chowdhury *et al.* [2] found that 49.8% of deaths could be attributed to PCa, 17.8% to cardiovascular disease, 11.6% to other cancers and 20.7% to other causes. A number of studies have estimated the relative burden of PCa mortality and summarised various prognostic factors in PCa. Shukla *et al.* [3] showed that 10-year PCa-specific mortality (PCSM) was significantly higher in metastatic (M1) PCa compared with non-metastatic stage IV PCa. A nationwide cancer registry study from Denmark [4] concluded that most men who eventually died from PCa had node-positive (N+) disease or M1 PCa at diagnosis. Additionally, a small cohort study from France [5] retrospectively showed that about half the patients who die from metastatic castration-resistant PCa had detectable distant metastases at diagnosis. Rider *et al.* [6] showed that risk stratification and the Charlson comorbidity index bear significant correlation with mortality rates in PCa patients treated with non-curative intent. However,

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none of these studies was carried out in the North American population and describe the hazards of PCa-specific death in the advanced PCa groups. We therefore carried out a population-based study using the Surveillance, Epidemiology and End Results (SEER) database, the primary aim being to characterise the presenting characteristics of those who ultimately died from PCa and to describe the association of risk groups with PCSS over a 25-year period.

Materials and Methods

The SEER Program database of the National Cancer Institute provides population-based cancer incidence and survival data for about one-third of the population of the USA [7]. The database was searched for all patients diagnosed with prostate adenocarcinoma as their first primary malignancy between 1 January 1990 and 31 December 2015. Demographic and clinicopathological data were collected, including date of diagnosis, age at diagnosis, ethnicity, clinical tumour (T), nodal (N) and metastatic (M) stage at time of diagnosis, baseline serum prostate-specific antigen (PSA) and biopsy Gleason score or grade. Information related to the date and cause of death were gathered to estimate PCSS. Based on features at the time of diagnosis, patients were assigned to the following clinical risk groups: low-risk localised (LRL), intermediate-risk localised (IRL), high-risk localised (HRL), N+ and M1 [8]. For cases diagnosed before 2004, information related to PSA and Gleason score were unavailable; for these cases, patients with cT1-T2a N0 M0 and low-grade carcinoma on biopsy were classified as LRL, those with cT3-4 N0 M0 or high-grade carcinoma were classified as HRL and all others with node-negative, non-metastatic disease were classified as IRL. For patients with localised PCa diagnosed in 2004 and thereafter, the original three-group risk stratification scheme of the National Comprehensive Cancer Network was used [8]. Data on primary modality of local treatment were also collected using the SEER Custom Database [9]. Primary local treatment was identified using the 'site-specific surgery' and 'radiation therapy' fields, as previously reported [10,11]. Descriptive statistics were used to characterise the risk group distribution of the overall study population and the risk group distribution of those who ultimately died from PCa. The median follow-up duration with interquartile range (IQR) was estimated using the reverse Kaplan–Meier method. PCSS was estimated using the Kaplan–Meier product limit method and PCSS among the risk groups was compared using the Log-rank test. Univariate and multivariate Cox proportional hazards models were used to identify the association of risk group with PCSS after adjustment for age at diagnosis, ethnicity, year of diagnosis and primary treatment modality. Corresponding unadjusted and adjusted hazard ratios together with 95% confidence intervals were reported. All statistical analyses were carried out using SPSS version 21 (IBM Corporation, NY, USA) and R statistical package version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), with a two-sided significance level set at $P < 0.05$.

Results

Patients

In total, 811 487 cases of PCa were identified from the SEER database for the study period. Sufficient data for risk group determination and cause of death were present in 635 733 cases (78.4%). The median age of the study population was 66 years (IQR 60–73 years).

Of the 635 733 patients who constituted the evaluable study population, 168 348 (26.5%) patients underwent primary radical prostatectomy, whereas 214 737 (33.8%) patients received primary radiotherapy. Information on radiotherapy was missing in 9283 (1.5%) patients and 5083 (0.8%) patients refused radiotherapy despite it being recommended as the primary treatment. In total, 9586 (1.5%) patients had both surgery and radiotherapy; 13 433 (2.1%) patients underwent local ablative procedures, including but not limited to, transurethral resection of prostate, cryotherapy, laser ablation, hyperthermia, segmental or subtotal prostatectomy, suprapubic prostatectomy or a combination of these local treatments; 5800 (0.9%) patients received radiotherapy in addition to these local therapies. In 209 463 (32.9%) patients, radiotherapy or surgery was not given or there was no information about local treatment in the SEER database. The risk group distribution of patients treated with primary radical prostatectomy was as follows: LRL 3.6%, IRL 50.0%, HRL 44.1%, N+ 2.2% and M1 0.1%. Among patients treated with primary radiotherapy, the risk group distribution was as follows: LRL 9.9%, IRL 57.1%, HRL 30.3%, N1 0.8% and M1 1.9%. The median follow-up for the study population was 83 months (IQR 42–136 months). At this follow-up, 448 375 (71%) patients were alive, whereas 187 358 (29%) had died. Of these deaths, 55 128 (30%) were attributed to PCa.

Risk Group Distribution of Those Diagnosed with Prostate Cancer and Those with Lethal Prostate Cancer

The overall risk group distribution of the patients was as follows: LRL 10.5% ($n = 66\,959$), IRL 49.7% ($n = 316\,227$), HRL 34.8% ($n = 221\,494$), N+ 1.5% ($n = 9150$) and M1 3.5% ($n = 21\,903$). The proportion of patients who died from PCa in the five risk groups was as follows: 3.2%, 5.1%, 10.2%, 19% and 57.2%, respectively. Considering those who died from PCa, the risk group distribution was as follows: LRL 3.9% ($n = 2152$), IRL 29.4% ($n = 16\,184$), HRL 40.9% ($n = 22\,530$), N+ 3.2% ($n = 1743$) and M1 22.8% ($n = 12\,519$). The risk group distribution of patients who died from PCa in 2015 ($n = 1823$), for which there was 25 years of follow-up and thus deaths from even the most indolently progressing cases were captured, was as follows: M1 23.8%, N+ 4.4%, HRL 40.9%, IRL 27.7% and LRL 3.2%. The year of diagnosis

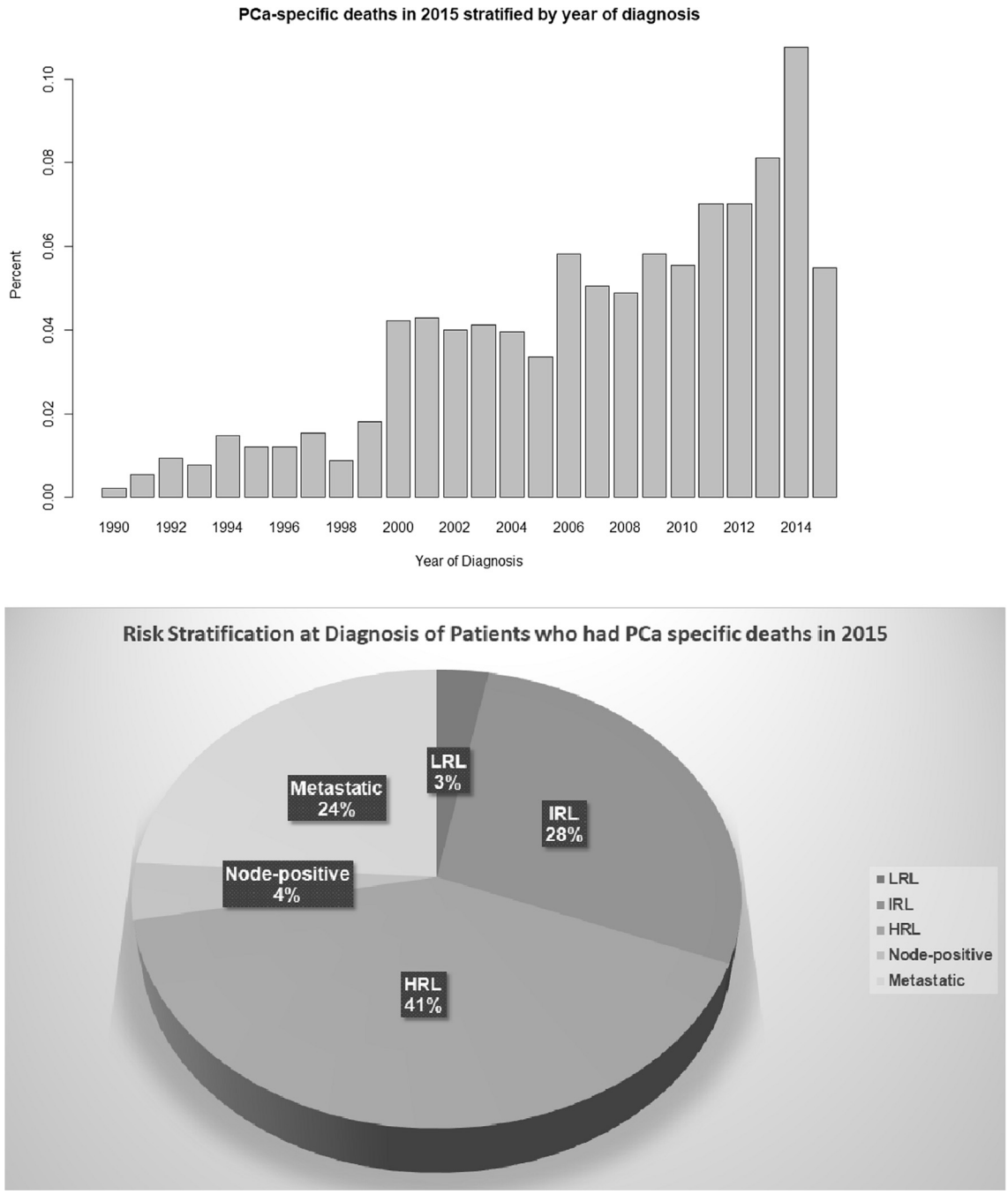

Fig 1. Year of diagnosis and risk group distribution of patients who died from prostate cancer in 2015.

together with the risk group distribution of patients who died in 2015 are shown in Figure 1.

PCSS for the entire study population at 10, 15 and 20 years was 89.1% (95% confidence interval 89–89.2%), 83.3% (95% confidence interval 83.2–83.5%) and 77.1% (95% confidence interval 76.8–77.4%), respectively (Figure 2). PCSS at 20 years was 84.8% (95% confidence interval 84–85.6%) for LRL, 83.6% (95% confidence interval 83.2–84%) for IRL, 71.2% (95% confidence interval 70.6–71.7%) for HRL, 47.7% (95% confidence interval 44.7–50.8%) for N+ and 10.3% (95% confidence interval 9.2–11.5%) for M1. Compared with patients with LRL disease, the unadjusted hazard ratio for PCSS was 1.21 in patients with IRL (95% confidence interval 1.16–1.27), 2.14 (95% confidence interval 2.78–3.04) with HRL, 7.14 (95% confidence interval 6.70–7.61) with N+ and 43.76 (95% confidence interval 41.79–45.82) with M1 PCa (Table 1). The adjusted hazard ratio for PCSS in IRL, HRL, N+ and M1 groups were 1.40 (95% confidence interval 1.33–1.46), 3.76 (95% confidence interval 3.60–3.93), 11.87 (95% confidence interval 11.14–12.65) and 37.12 (95% confidence interval 35.43–38.88), respectively (Table 1). Treatment with radiotherapy and radical prostatectomy was associated with a 16 and 72% reduction, respectively, in the relative risk of PCa-related deaths compared with no treatment.

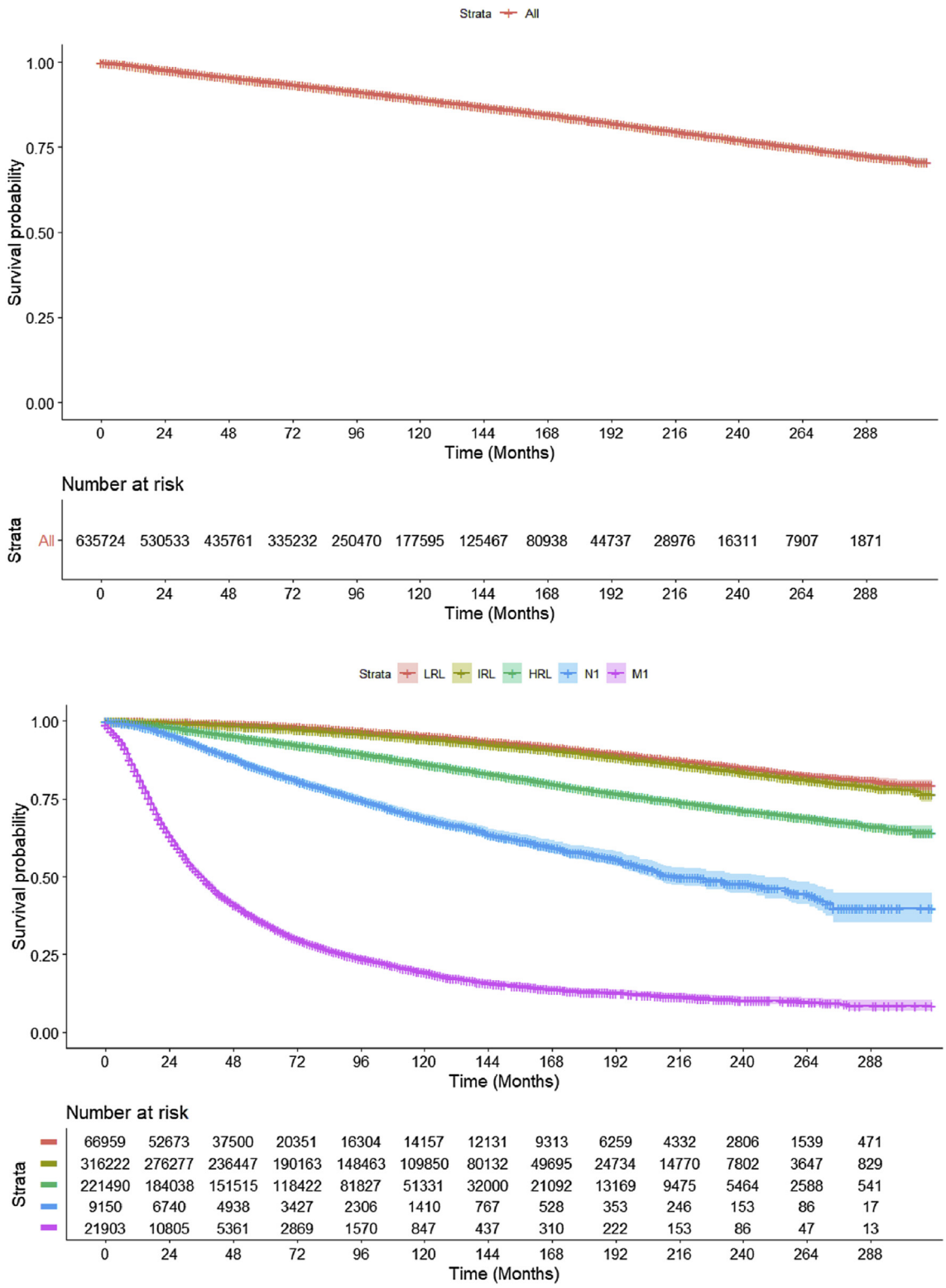

Fig 2. Prostate cancer-specific survival of the study population stratified by risk groups.

Discussion

The current study of a very large population with long-term follow-up highlights several important findings. It shows the incidence of and death from PCa over a period of 25 years in the American population and underscores the negative prognostic association of advanced disease with PCSS after adjusting for other potential prognostic factors, including age at diagnosis, ethnicity and use of local treatment in the form of radical prostatectomy or radiotherapy. The risk group distribution of the patients who died over this period of 25 years is subject to follow-up bias.

Table 1
Univariate and multivariate analysis for prognostic factors

Factors		Univariate hazard ratio (95% confidence interval)	*P* value	Multivariate hazard ratio (95% confidence interval)	*P* value
Age		1.072 (1.071–1.073)	<0.001	1.045 (1.044–1.046)	<0.001
Ethnicity	White	1		1	
	Black	1.27 (1.23–1.30)	<0.001	1.27 (1.24–1.31)	<0.001
	Native Indians	1.26 (1.07–1.48)	0.005	1.27 (1.08–1.49)	0.004
	Asian/Pacific Islanders	0.62 (0.61–0.64)	<0.001	0.70 (0.68–0.72)	<0.0004
	Unspecified/unknown	0.48 (0.41–0.55)	<0.001	0.55 (0.47–0.64)	
Year of diagnosis	1990–1998	1		1	
	1999–2006	0.46 (0.45–0.47)	<0.001	0.91 (0.89–0.94)	<0.001
	2007–2015	0.40 (0.39–0.41)	<0.001	0.87 (0.84–0.91)	<0.0008
Radiotherapy	No	1	<0.001	1	<0.001
	Yes	0.84 (0.82–0.85)		0.84 (0.83–0.86)	
Surgery	No	1	<0.001	1	<0.001
	RP	0.46 (0.45–0.47)		0.28 (0.27–0.29)	
Risk groups	LRL	1		1	
	IRL	1.21 (1.16–1.27)	<0.001	1.40 (1.33–1.46)	<0.001
	HRL	2.91 (2.78–3.04)	<0.001	3.76 (3.60–3.93)	<0.001
	Node-positive	7.14 (6.70–7.61)	<0.001	11.87 (11.14–12.65)	<0.001
	Metastatic	43.76 (41.79–45.82)	<0.001	37.12 (35.43–38.88)	<0.001

LRL, low-risk localised; IRL, intermediate-risk localised; HRL, high-risk localised; RP, radical prostatectomy.

Specifically, patients diagnosed recently have a relatively shorter follow-up duration. This might result in overestimation of the proportion of deaths accounted for by patients presenting with advanced disease whose cancers have a shorter natural history. To minimise this bias, we have separately reported here the risk group distribution of those patients who died in the final year of the study period – 2015 – for which 25 years of follow-up was available.

The findings of our study are broadly consistent with those of other recent population-based studies conducted elsewhere [2–6]. Shukla *et al.* [3] reported PCSM for men diagnosed with various presentations of PCa and examined the adequacy of the current American Joint Committee on Cancer (AJCC) staging system. They concluded that PCSM at 10 years was 5% for localised disease, 7% for T3a, 14% for T3b, 26% for T4, 27% for N1 and 66% for M1 cancers. Another study by Helgstrand *et al.* [4] described the characteristics of patients (n = 19 487) who died from PCa in Denmark between 1995 and 2013. Overall, 46.9%, 16.8% and 36.3% had M1, locally advanced/N+ and localised disease, respectively, at diagnosis. Only 0.15% had LRL PCa, probably reflecting a lower uptake of PSA screening in the Danish population over this period. In the study by Patrikidou *et al.* [5], 61% of patients with castration-resistant metastatic PCa (n = 190) treated between 2008 and 2011 eventually died from PCa (n = 113); in retrospect, 56% of these 113 patients had *de novo* M1 disease. Among patients who had localised PCa at diagnosis, most were high risk. Almost half the deaths in a large UK registry of men diagnosed with PCa were attributed to their cancer. Patients with *de novo* M1 disease accounted for 44.5% of all deaths from PCa, despite constituting only about 14% of the overall registry population [2].

This study is subject to a number of limitations. First, adequate information for risk categorisation was absent in about 22% of patients and before 2004 risk stratification was an approximation based on TNM staging and biopsy grade instead of PSA and Gleason score, as these data were not recorded in the SEER database in this period. One of the potential consequences of this is misclassification bias. Additionally, this analysis could not account for the migration in Gleason scores that has occurred over the study period [12,13]. As a result of this, a proportion of the patients diagnosed in the early years of the study period classified as having LRL PCa would today have been considered to have IRL PCa. This might have translated into exaggeration of PCa mortality burden in patients with LRL PCa. Nonetheless, PCa-specific death remains remarkably low in LRL patients in our study.

The study period extended back to the era before widespread uptake of PSA screening. The prevalence of PCa increased markedly after the advent of PSA screening and most of these cases are mainly restricted to LRL and IRL disease. Therefore, the correlation of year of diagnosis with PCSS might carry a residual artefact of the influence of PSA screening on PCSS. Similarly, there have been significant technical improvements in imaging modalities used to identify metastatic PCa over the study period [14,15]. Some of those diagnosed with HRL PCa might have been upstaged to N+/M1 with the use of more advanced contemporary imaging techniques and therefore this would have had a positive influence on the PCSS of both the localised group and the advanced N+/M1 group. Finally, studies conducted over such a long duration are subject to underlying confounding due to evolution of treatment over time. There has been significant progress in the treatment of PCa over the last decade, with randomised trials showing improvements in overall survival with local treatment [16–20] as well as systemic treatment of advanced PCa, including metastatic

hormone-sensitive [21–24] and castration-resistant disease [25–30]. One must, therefore, consider the results of our study in light of advances in local and systemic therapies.

Although not a primary aim of this study, a sizeable difference was identified in the hazard ratios for PCSS associated with receipt of radical prostatectomy and radiotherapy in this analysis. Caution is required in the interpretation of this finding. First, the treatment intent of radiotherapy (curative versus palliative) cannot be ascertained from the SEER database and thus a proportion of those treated with primary radiotherapy received palliative rather than radical courses of therapy. Second, the SEER database is not annotated with respect to numerous important covariates, including information on performance status, comorbidity, systemic therapies, volume of nodal and metastatic disease, access to treatment, sequence of treatment and others. Any comparison of the efficacy of these two local treatment modalities will probably be confounded by unknown differences in these covariates, and it is emphasised that this study was not designed to draw such comparisons. It is finally noted that the risk group distributions of patients treated with radical prostatectomy and radiotherapy were substantially dissimilar.

Despite these limitations, the current study shows that in a large contemporary cohort, patients with HRL, N+ or M1 PCa comprise only about 40% of those diagnosed with PCa. However, these subgroups account for about two-thirds of deaths from PCa. Compared with low-risk organ-confined PCa, metastatic disease carries an approximately 40-fold increased risk of death from PCa over time. Our findings emphasise that the efforts to reduce the overall mortality burden of PCa will largely depend on improvements in the treatment of high-risk, N+ and metastatic disease. By contrast, active treatment of low-risk patients will have negligible impact on the overall mortality burden of PCa.

Conflict of Interest

The authors declare no conflicts of interest in relation to this work.

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