BJUI
BJU International

Association between very small tumour size and increased cancer-specific mortality after radical prostatectomy in lymph node-positive prostate cancer

Vinayak Muralidhar, Brandon A. Mahal*, Michelle D. Nezolosky†, Clair J. Beard†, Felix Y. Feng‡, Neil E. Martin†, Jason A. Efstathiou§, Toni K. Choueiri¶, Mark M. Pomerantz¶, Christopher J. Sweeney¶, Quoc-Dien Trinh**, Matthew G. Vander Heiden†† and Paul L. Nguyen†

*Harvard-MIT Division of Health Sciences and Technology, *Harvard Medical School, †Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA, ‡Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, §Department of Radiation Oncology, Massachusetts General Hospital, ¶Department of Medical Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, **Department of Urology, Brigham and Women's Hospital, Boston, and ††Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA*

Objective

To determine whether very small prostate cancers present in patients who also have lymph node (LN) metastases represent a particularly aggressive disease variant compared with larger LN-positive tumours.

Patients and Methods

We identified 37 501 patients diagnosed with prostate cancer between 1988 and 2001 treated with radical prostatectomy within the Surveillance, Epidemiology, and End Results database. The primary study variables were tumour size by largest dimension (stratified into: (i) microscopic focus only or 1 mm; (ii) 2–15 mm; (iii) 16–30 mm; (iv) >30 mm), regional LN involvement, and the corresponding interaction term. We evaluated the risk of 10-year prostate cancer-specific mortality (PCSM) using the Fine and Gray model for competing risks after controlling for race, tumour grade, T stage, receipt of radiation, number of dissected LNs, number of positive LNs, year of diagnosis, and age at diagnosis.

Results

The median follow-up was 11.8 years. There was a significant interaction between tumour size and LN involvement (P-interaction <0.001). In the absence of LN involvement (36 561 patients), the risk of 10-year PCSM increased monotonically with increasing tumour size. Among patients with LN involvement (940), those with the smallest tumours had increased 10-year PCSM compared with patients with tumours sized 2–15 mm (24.7% vs 11.8%; adjusted hazard ratio [AHR] 2.84, 95% confidence interval [CI] 1.21–6.71; $P = 0.017$) or 16–30 mm (24.7% vs 15.5%; AHR 3.12, 95% CI 1.51–6.49; $P = 0.002$), and similar 10-year PCSM as those with tumours >30 mm (24.7% vs 24.9%; $P = 0.156$).

Conclusion

In patients with prostate cancer with LN involvement, very small tumour size may predict for higher PCSM compared with some larger tumours, even after controlling for other prognostic variables. These tumours might be particularly aggressive, beyond what is captured by pathological assessment of tumour grade and stage.

Keywords

prostate cancer, tumour size, node-positive prostate cancer, microscopic tumour

Introduction

The prognosis of prostate cancer depends on multiple factors, including PSA, Gleason grade, and T stage, which comprise the American Joint Committee on Cancer (AJCC) 7th edition risk group classification [1]. Other factors have also been associated with prostate cancer prognosis, such as patient age, race, and marital status [2,3]. In addition, larger tumours

BJU International © 2015 BJU International | doi:10.1111/bju.13248
Published by John Wiley & Sons Ltd. www.bjui.org

have been associated with an increased risk of prostate cancer-specific mortality (PCSM) [4,5]. However, among tumours that have given rise to lymph node (LN) metastasis, it is unknown whether very small primary tumours, which might have acquired metastatic potential relatively early in the course of cancer progression, represent more aggressive disease than larger tumours. We sought to determine whether tumour size paradoxically interacts with LN involvement among patients with prostate cancer treated with radical prostatectomy (RP). We hypothesised that among patients with LN involvement, tumour size and PCSM would be related by a 'U' shape, such that those with very small tumours would be at increased risk of PCSM compared with those with larger tumours and similar risk as those with much larger tumours.

Patients and Methods

The Surveillance, Epidemiology, and End Results (SEER) programme is sponsored by the National Cancer Institute and collects cancer incidence, diagnostic, and treatment-related information from up to 18 registries, covering 28% of the USA population starting in 1973 [6]. Using the SEER database, we identified 37 501 patients diagnosed with prostate cancer between 1988 and 2001 who were treated with RP and who had known tumour size data. The years of inclusion were selected because detailed tumour size was not recorded before 1988 and we wished to allow for at least 10 years of follow-up (survival data for the current edition of SEER ends in 2011). Patients were only included if they had undergone RP in order to allow for accurate assessment of tumour size; for patients who were treated with RP, the SEER database records tumour size according to the longest dimension of the primary tumour listed on the pathology report [7]. This study was approved by the Institutional Review Board.

For all statistical analyses, Stata/MP 13.1 (StataCorp, College Station, TX, USA) was used. The primary study variables were tumour size by largest dimension, regional LN involvement, and the corresponding interaction term. To allow for statistical comparison between groups, patients were stratified according to the following pre-determined size strata: (i) microscopic focus only or 1 mm; (ii) 2–15 mm; (iii) 16–30 mm; (iv) >30 mm. Size strata were determined such that the first group contained the smallest possible tumours recorded in the SEER database, and the remaining three groups were equally spaced and divided the LN-positive cohort into roughly three equal sizes.

The median follow-up was compared using the log-rank test [8]; other baseline characteristics were compared using the two-sample *t*-test on proportions or chi-squared test, as appropriate. Using patients with tumours sized 2–15 mm as the referent group, we evaluated the risk of 10-year PCSM using the Fine and Gray model [9] for competing risks between pairs of strata after controlling for tumour grade (Gleason score ≤7 vs 8–10), race, age at diagnosis, year of diagnosis (1988–1994 vs 1995–2001), number of LNs positive, number of LNs dissected (<6 vs ≥6 LNs), T stage, and receipt of radiation treatment. When we compared the PCSM of patients with the smallest tumours (microscopic focus only or 1 mm) to the PCSM of those with tumours sized 16–30 mm or >30 mm, the group with the larger tumours was chosen as the referent group. We also modelled the impact of an interaction term, obtained by multiplying LN status with tumour size. To evaluate tumour size as a continuous variable, we also fitted a quadratic competing risks model in tumour size over the range 1–15 mm, adjusting for the same variables as prior. This range was chosen because we hypothesised that the descending part of the U-shape between tumour size and PCSM would occur over the small range 1–7 mm including only ≈10% of patients; if a much wider range were chosen (e.g. 1–100 mm), a monotonic function that ignores this descending portion could spuriously appear to have a good fit of the data if it closely modelled only the ascending portion of the U-shape, where a majority of the data points (patients) lie.

Finally, we conducted a sensitivity analysis to determine whether the relationships we observed were robust to changing the thresholds between strata by up to 5 mm in either direction, keeping the definition of the smallest group fixed.

Results

Baseline Characteristics

The median follow-up was 11.8 years. There were 36 561 patients with LN-negative disease and 940 patients with LN-positive disease. Patients with LN-positive disease tended to have larger primary tumours, higher grade disease, an earlier year of diagnosis, higher T stage, and more LNs examined than those with LN-negative disease (Table 1; $P < 0.001$). About 22.8% of patients with LN-negative disease and 6.0% of patients with LN-positive disease were in the smallest size stratum. There were no significant differences in age or racial composition of patients with LN-negative or LN-positive disease (Table 1). In all, 4.8% of patients with LN-negative and 23.8% of patients with LN-positive disease died from prostate cancer.

Very Small Prostate Cancers are Associated with Increased PCSM among LN-Positive Patients

There was a significant interaction between tumour size and LN involvement (*P*-interaction <0.001; Figs 1–3). Among LN-positive cases, tumours that were very small (microscopic foci

Table 1 Baseline patient characteristics.

Patient characteristic	All patients	LN-negative	LN-positive	*P*
No. patients	37 501	36 561	940	
Median (IQR) follow-up, years	11.8 (10–14.9)	11.8 (10–14.9)	11.2 (6.8–14.6)	<0.001
N (%)				
Year of diagnosis				
1988–1994	10 394 (27.7)	9 940 (27.2)	454 (48.3)	<0.001
1995–2001	27 107 (72.3)	26 621 (72.8)	486 (51.7)	
Patient age, years				
≤65	18 894 (50.4)	18 842 (51.5)	472 (50.2)	0.431
>65	18 607 (49.6)	17 719 (48.5)	468 (49.8)	
Race				
White	32 025 (85.4)	31 222 (85.4)	803 (85.4)	0.421
Black	3 269 (8.7)	3 177 (8.7)	92 (9.8)	
Other	2 037 (5.4)	1 992 (5.4)	45 (4.8)	
Unknown	170 (0.5)	170 (0.5)	0	
Tumour size, mm				
Microscopic focus only or 1 mm	8 378 (22.3)	8 322 (22.8)	56 (6.0)	<0.001
2–15	16 662 (44.4)	16 413 (44.9)	249 (26.5)	
16–30	8 784 (23.4)	8 467 (23.2)	317 (33.7)	
>30	3 677 (9.8)	3 359 (9.2)	318 (33.8)	
Gleason score				
≤7	30 536 (81.4)	30 054 (82.2)	482 (51.3)	<0.001
>7	6 390 (17.0)	5 944 (16.3)	446 (47.4)	
Unknown	575 (1.5)	563 (1.5)	12 (1.3)	
T stage				
T1	12 790 (34.1)	12 669 (34.7)	121 (12.9)	<0.001
T2	19 197 (51.2)	18 800 (51.4)	397 (42.2)	
T3	4 336 (11.6)	3 990 (10.9)	346 (36.8)	
T4	288 (0.8)	259 (0.7)	29 (3.1)	
Unknown	890 (2.4)	843 (2.3)	47 (5.0)	
Number of dissected LNs				
≤6	21 181 (56.5)	20 932 (57.3)	249 (26.5)	<0.001
>6	10 912 (29.1)	10 364 (28.3)	548 (58.3)	
Unknown	5 408 (14.4)	5 265 (14.4)	143 (15.2)	
Median number of lymph nodes positive (IQR)	0 (0-0)	0 (0-0)	1 (1-2)	<0.001

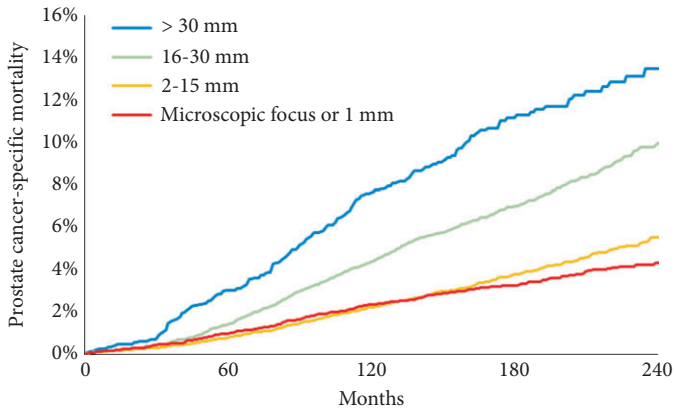
IQR, interquartile range. P values correspond to differences between LN-negative and LN-positive patients.

only or 1 mm) conferred an increased risk of 10-year PCSM compared with tumours that were sized 2–15 mm (24.7% vs 11.8%; adjusted hazard ratio [AHR] 2.84, 95% CI 1.21–6.71; $P = 0.017$) or 16–30 mm (24.7% vs 15.5%; AHR 3.12, 95% CI 1.51–6.49; $P = 0.002$), even after controlling for multiple patient-specific factors, including tumour grade and receipt of radiation treatment. Patients with very small tumours had similar 10-year PCSM as those with tumours that were >30 mm (24.7% vs 24.9%; $P = 0.156$).

In contrast, among patients with LN-negative disease, tumour size correlated directly with PCSM. Very small tumours (microscopic focus or 1 mm) and small tumours (2–15 mm) had similarly low 10-year PCSM (2.4% vs 2.2%; $P = 0.016$), and 10-year PCSM rose with tumour size for those with tumours that were 16–30 mm or >30 mm (4.4% and 7.7%, respectively; $P < 0.001$).

Multivariable analysis using patients with the smallest LN-negative tumours as the referent group confirmed the relationship between very small tumour size and worse PCSM among LN-positive patients and also showed an increased risk of PCSM with earlier year of diagnosis, older age, higher tumour grade, more involved LNs, lack of radiation treatment, and increasing T stage (Table 2).

Fig. 1 PCSM over time among LN-negative patients with prostate cancer by the longest dimension of the primary tumour.



Similarly, modelling tumour size as a continuous variable using a quadratic and linear term confirmed the U-shaped relationship between tumour size and PCSM among LN-

Fig. 2 PCSM over time among LN-positive patients with prostate cancer by the longest dimension of the primary tumour.

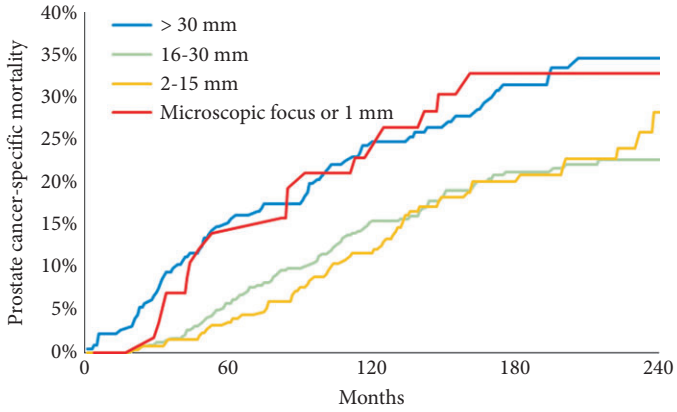
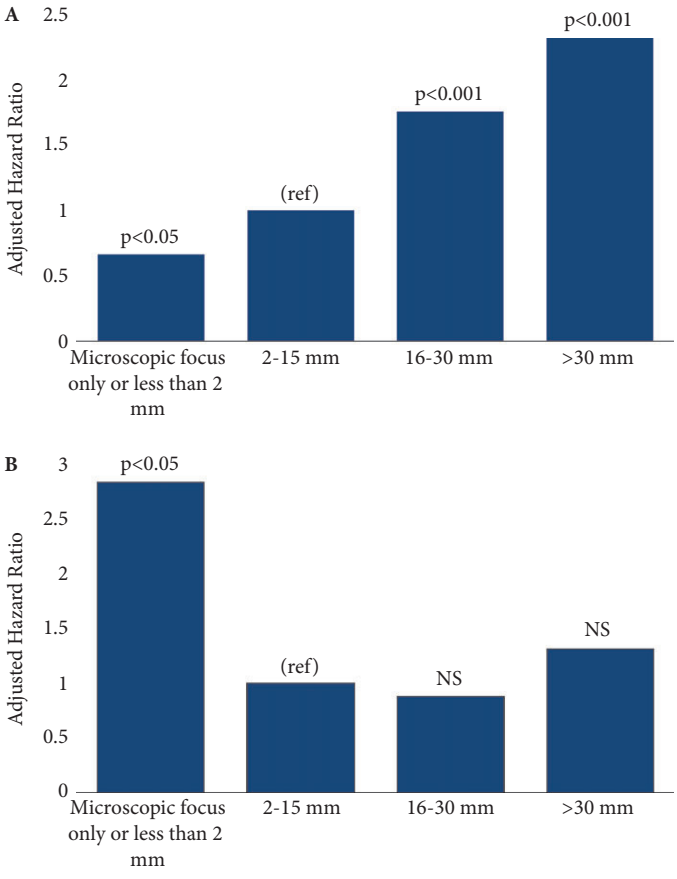


Fig. 3 Adjusted hazard ratios for PCSM among patients with LN-negative (**A**) and LN-positive (**B**) prostate cancer by the longest dimension of the primary tumour. NS, not significant.



positive patients, with both the squared term and linear terms significantly associated with PCSM (AHR 1.02, $P = 0.003$; and AHR 0.66, $P = 0.002$, respectively). This model predicts a decrease in PCSM between tumour sizes of 1 and 9 mm with a local minimum at 9 mm before PCSM begins to rise with tumour size. There was no such significant relationship among LN-negative cases.

Table 2 Multivariable competing risks regression for PCSM including year of diagnosis, age, race, Gleason score, number of dissected LNs, number of positive LNs, receipt of radiation therapy, T stage, tumour size and nodal status. For analysis of tumour size and nodal status, patients with the smallest LN-negative tumours were chosen as the referent group.

Variable	HR (95% CI)	*P*
Year of diagnosis		
1988–1994	1.00	
1995–2001	0.81 (0.67–0.97)	0.023
Patient age, years		
≤65	1.00	
65	1.18 (1.03–1.34)	0.014
Race		
White	1.00	
Black	1.03 (0.81–1.31)	0.791
Other	0.67 (0.48–0.93)	0.017
Gleason score		
≤7	1.00	
>7	2.71 (2.35–3.11)	<0.001
Number of dissected LNs		
≤6	1.00	
>6	0.96 (0.83–1.09)	0.507
Number of positive LNs (increasing)	1.09 (1.02–1.16)	0.008
Receipt of radiation therapy		
No	1.00	
Yes	1.69 (1.40–2.05)	<0.001
T stage		
T1	1.00	
T2	1.51 (1.24–1.83)	<0.001
T3	1.93 (1.47–2.52)	<0.001
T4	2.54 (1.60–4.04)	<0.001
Tumour size and LN status		
Microscopic focus only or 1 mm, N0	1.00	
2–15 mm, N0	1.39 (1.01–1.92)	0.044
16–30 mm, N0	2.51 (1.83–3.45)	<0.001
>30 mm, N0	3.41 (2.41–4.82)	<0.001
Microscopic focus only or 1 mm, N1	16.72 (8.12–34.41)	<0.001
2–15 mm, N1	4.95 (3.11–7.87)	<0.001
16–30 mm, N1	4.59 (2.99–7.05)	<0.001
>30 mm, N1	6.68 (4.12–10.82)	<0.001

Finally, in a sensitivity analysis, we observed a similar statistically significant U-shaped relationship between tumour size and the adjusted risk of PCSM when the threshold for the size strata were changed by up to 5 mm in either direction (data not shown).

Discussion

In the present study, we provide the first evidence that tumour size and LN status may interact to provide prognostic information for patients with prostate cancer treated with RP. In particular, we found that among men with LN-positive disease, very small primary tumours were associated with nearly double the risk of PCSM compared with tumours sized 2–15 mm or 16–30 mm, even after adjusting for potential explanatory factors such as tumour grade, race, and number of involved LNs. On the other hand, among those with LN-negative disease, the risk of PCSM increased monotonically with tumour size. These findings were confirmed when

modelling tumour size as a continuous quadratic variable. Our present findings raise the intriguing possibility that small LN-positive prostate cancers represent a unique and more aggressive disease process compared with larger LN-positive tumours. These results challenge the notion that increasing tumour bulk is associated with equal or worse outcomes in the setting of LN-positive prostate cancer [10,11].

This finding has important implications for researchers and clinicians. First, the present study may provide insights into the unique biology of some prostate cancers to motivate further research. The traditional view of cancer spread is that cells within the primary tumour acquire additional mutations as the tumour grows to a larger size, increasing the likelihood that some cells acquire requisite mutations for colonisation of regional LNs and eventually spread to distant sites [12,13]. Consistent with this model, early events in the development of prostate cancer are thought to include mutations in genes that regulate proliferation, differentiation, and apoptosis [14]. However, our present results suggest that in patients with evidence of LN spread, the presence of a very small primary tumour within the prostate may signify relatively early acquisition of genetic changes that enable spread to regional or distant sites. Alternatively, these prostate cancers may represent cancers with higher mutation rates that allow for more rapid selection of a clone capable of LN metastasis. Either way, such small tumours may represent biologically aggressive cancers. The difference in PCSM between very small and larger LN-positive tumours was present after adjusting for tumour grade and T stage, which suggests that the increased biological aggressiveness of very small LN-positive tumours may provide prognostic information beyond what is captured by pathological assessment of T stage and size. Uncovering the biological underpinnings of small tumours associated with LN involvement might lead to the discovery of new genomic changes in this subset of tumours or to the discovery of new drug targets or prognostic markers.

Second, even though it is likely that many patients with LN-positive disease will receive aggressive therapy, our present results emphasise that aggressive adjuvant treatment, most likely with androgen-deprivation therapy [15,16], might be especially important for those with very small primary tumours. The presence of a very small primary tumour in the setting of LN involvement conferred an absolute increase in the risk of 10-year PCSM of 12.9% compared with larger (2–15 mm) tumours; this risk increase was larger than the 7.4–11.1% absolute difference in 10-year PCSM between LN-positive tumours sized 2–30 mm and similarly sized LN-negative tumours. Therefore, the presence of a very small primary tumour in the setting of LN involvement may represent an even more adverse prognostic factor than the presence of LN involvement alone. While we did not study the role of adjuvant treatment, our present data might still be used by physicians to counsel patients with very small LN-positive tumours about prognosis and to guide therapy decisions.

Previous studies have identified increasing prostate tumour volume as a negative prognostic factor in organ-confined disease and increasing LN tumour volume as a negative prognostic factor in LN-positive disease [4,5,17–20]. In the LN-positive setting, others have shown that increasing T stage is associated with worse outcomes [10,11], but there are no studies to our knowledge that have studied the prognostic role of very small prostate cancer size in LN-positive disease. However, others have previously suggested that small tumour foci might be aggressive precursors of metastatic spread even compared with larger tumours. In a recent case report, Haffner et al. [21] used whole-genome sequencing and molecular analyses to trace the lineage of the cell clone that ultimately gave rise to metastatic disease in a patient who died from prostate cancer. The molecular features of the metastatic foci suggested that the lethal clone originated from a small area of low-grade disease, rather than the larger, higher grade focus of cancer found elsewhere within the prostate and within involved regional LNs. This finding, similarly to the present study, suggests that even small tumours can be potentially lethal, which raises the possibility that the largest lesion in a tumour may not be the most dangerous, a concept which might have implications for focal therapy [22]. A similar relationship between very small tumour size and increased mortality has also been seen in LN-positive breast cancer [23]. It is possible that similar biological mechanisms might underlie the U-shaped relationship between tumour size and CSM across different cancer types.

The results of our multivariable analysis are in agreement with the work of others, including increased PCSM with: earlier year of diagnosis [24], due to differences in follow-up or changes in treatment; more involved LNs [10]; higher grade disease [1]; and lack of adjuvant radiation in the LN-positive setting [25]. We did not find that the number of dissected LNs had an impact on outcome, consistent with prior work [26,27], although some have found an association between the number of examined LNs and outcomes in select situations [28,29]. We did not find a relationship between Black race and increased PCSM, in contrast to some prior research [30], although others have found that racial disparities in outcomes might be partially explained by adjustment for stage at diagnosis, treatment received, and other clinical and demographic factors, including access to care [31,32].

Our present study had some limitations. First, there are multiple potential confounders for which we could not control. For example, due to limitations in the SEER database, we were not able to obtain data on the PSA level at

diagnosis or the presence of other adverse features (e.g. perineural invasion) for our cohort. Similarly, for the years of inclusion in our study, the SEER database recorded tumour grade as 'moderately differentiated' (low/intermediate grade) for Gleason score 5–7 and 'poorly differentiated' (high grade) for Gleason score 8–10; the actual Gleason scores were not recorded for the patients in our present study. It is possible that consideration of Gleason score 7 as high grade or analysis of Gleason score 8 as separate from Gleason 9–10 could explain part of the relationship between very small tumour size and increased PCSM. Our present results should be interpreted with caution until future studies in more detailed clinical datasets can validate our findings after adjusting for these additional factors.

Second, our present study was retrospective and has the general limitations of this study design, including susceptibility to selection bias. For example, patients with small primary tumours might have been less likely to be diagnosed or experienced delayed diagnosis due to having lower serum PSA levels than those with larger tumours; however, all patients with LN-positive disease probably had elevated PSA levels due to relatively high tumour volume regardless of the size of the primary tumour. Therefore, the impact of small primary tumour size on the rate or timing of diagnosis from PSA screening was probably small. For patients with LN-negative disease, while those with small tumours might have had delayed diagnosis, this bias would tend to overestimate the PCSM in this cohort, but they still had lower PCSM than patients with larger tumours. In addition, the differences in survival that we observed may be attributable to patients in the different study groups having received different interventions rather than to underlying differences in tumour biology or aggressiveness. However, we adjusted for receipt of radiation therapy, and patients with LN-positive disease are likely to have received similarly aggressive systemic therapy (i.e. androgen-deprivation therapy) regardless of the size of their primary tumours because management in this patient population would typically be dictated by the presence of LN involvement.

Third, we had relatively few patients in some of our groups, so the subset of patients with very small LN-positive tumours may represent a somewhat unique group. This limitation was inherent to our study design given the relative rarity of LN-positive prostate cancer. Although our present findings may therefore apply to only a subset of patients with prostate cancer, future research into the mechanisms of increased aggressiveness of very small LN-positive tumours could potentially benefit all patients with prostate cancer.

Fourth, we did not have centralised pathology review, and it is possible that there is significant heterogeneity in how the samples were handled and analysed. In addition, the SEER database has previously been reported to contain errors in recording of tumour size in other sites [33]. While such errors and differences in sample handling may reduce the reliability of our present results, they are likely to be random and therefore not systematically bias our analyses. Nevertheless, our present findings must be validated in other clinical datasets.

In conclusion, in the present study, we found that LN involvement paradoxically interacts with tumour size among patients with prostate cancer treated with RP. In the setting of LN involvement, very small prostate cancers were associated with approximately double the risk of PCSM as tumours sized 2–15 or 16–30 mm, whereas among LN-negative patients, PCSM rose monotonically with primary tumour size. If these findings are validated in other studies, future research should focus on understanding the biology of very small prostate cancers that give rise to LN involvement in order to elucidate the mechanisms underlying the aggressiveness of these tumours. A deeper understanding of the biology of these tumours might allow for more effective means of risk stratification and potentially lead to new therapies. Additionally, physicians could use these results to counsel patients with small primary tumours and LN involvement regarding their increased risk of PCSM and to guide therapy decisions.

Acknowledgements

This work was supported by grants from the Health Sciences and Technology IDEA2 Program supported by the Peter C. Farrell (1967) Fund, The Prostate Cancer Foundation, Fitz's Cancer Warriors, David and Cynthia Chapin, Hugh Simons in Honor of Frank and Anne Simons, The Scott Forbes and Gina Ventre Fund, and a grant from an anonymous family foundation.

Conflicts of Interest

Paul L. Nguyen has worked as a consultant for Medivation and GenomeDx. Quoc-Dien Trinh has been a speaker for Intuitive Surgical. The other authors have no conflicts to disclose.

References

1 **Edge S, Byrd DR, Compton CC, Green FL, Trotti A** eds. *AJCC Cancer Staging Manual*, 7th edn, New York: Springer, 2010
2 **Cooperberg MR**. Re-examining racial disparities in prostate cancer outcomes. *J Clin Oncol* 2013; 31: 2979–80
3 **Aizer AA, Chen MH, McCarthy EP et al.** Marital status and survival in patients with cancer. *J Clin Oncol* 2013; 31: 3869–76
4 **Vollmer RT**. Percentage of tumor in prostatectomy specimens: a study of American Veterans. *Am J Clin Pathol* 2009; 131: 86–91
5 **Vollmer RT**. Percentage of tumor and tumor length in prostate biopsy specimens: a study of American veterans. *Am J Clin Pathol* 2008; 130: 940–3
6 **Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)**. SEER*Stat Database: Incidence – SEER 9 Regs

Research Data, Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment> – Linked To County Attributes – Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission

7 **National Cancer Institute**. *SEER Training Modules, General Rules for Coding Tumor Size*. Available at: http://training.seer.cancer.gov/collaborative/system/tnm/t/size/rules.html. Accessed June 2015

8 **Kaplan EL, Meier P**. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53: 457–81

9 **Fine J, Gray R**. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509

10 **Abdollah F, Karnes RJ, Suardi N et al.** Predicting survival of patients with node-positive prostate cancer following multimodal treatment. *Eur Urol* 2014; 65: 554–62

11 **Daneshmand S, Quek ML, Stein JP et al.** Prognosis of patients with lymph node positive prostate cancer following radical prostatectomy: long-term results. *J Urol* 2004; 172: 2252–5

12 **Lodish H, Berk A, Zipursky SL et al.** (eds). *Molecular Cell Biology*, 4th edn. New York: W. H. Freeman, 2000: Section 24.1

13 **Nathanson SD**. Insights into the mechanisms of lymph node metastasis. *Cancer* 2003; 98: 413–23

14 **Shen MM, Abate-Shen C**. Molecular genetics of prostate cancer: new prospects for old challenges. *Genes Dev* 2010; 24: 1967–2000

15 **Messing EM, Manola J, Yao J et al.** Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol* 2006; 7: 472–9

16 **Wong YN, Freedland S, Egleston B, Hudes G, Schwartz JS, Armstrong K**. Role of androgen deprivation therapy for node-positive prostate cancer. *J Clin Oncol* 2009; 27: 100–5

17 **Kikuchi E, Scardino PT, Wheeler TM, Slawin KM, Ohori M**. Is tumor volume an independent prognostic factor in clinically localized prostate cancer? *J Urol* 2004; 172: 508–11

18 **Kim KH, Lim SK, Shin TY et al.** Tumor volume adds prognostic value in patients with organ-confined prostate cancer. *Ann Surg Oncol* 2013; 20: 3133–9

19 **Knoedler JJ, Karnes RJ, Thompson RH, Rangel LJ, Bergstralh EJ, Boorjian SA**. The association of tumor volume with mortality following radical prostatectomy. *Prostate Cancer Prostatic Dis* 2014; 17: 144–8

20 **Cheng L, Zincke H, Blute ML, Bergstralh EJ, Scherer B, Bostwick DG**. Risk of prostate carcinoma death in patients with lymph node metastasis. *Cancer* 2001; 91: 66–73

21 **Haffner MC, Mosbruger T, Esopi DM et al.** Tracking the clonal origin of lethal prostate cancer. *J Clin Invest* 2013; 123: 4918–22

22 **Giannarini G, Gandaglia G, Montorsi F, Briganti A**. Will focal therapy remain only an attractive illusion for the primary treatment of prostate cancer? *J Clin Oncol* 2014; 32: 1299–301

23 **Wo JY, Chen K, Neville BA, Lin NU, Punglia RS**. Effect of very small tumor size on cancer-specific mortality in node-positive breast cancer. *J Clin Oncol* 2011; 29: 2619–27

24 **Mitchell CR, Boorjian SA, Umbreit EC, Rangel LJ, Carlson RE, Karnes RJ**. 20-Year survival after radical prostatectomy as initial treatment for cT3 prostate cancer. *BJU Int* 2012; 110: 1709–13

25 **Abdollah F, Karnes RJ, Suardi N et al.** Impact of adjuvant radiotherapy on survival of patients with node-positive prostate cancer. *J Clin Oncol* 2014; 32: 3939–47

26 **DiMarco DS, Zincke H, Sebo TJ, Slezak J, Bergstralh EJ, Blute ML**. The extent of lymphadenectomy for pTXNO prostate cancer does not affect prostate cancer outcome in the prostate specific antigen era. *J Urol* 2005; 173: 1121–5

27 **Murphy AM, Berkman DS, Desai M, Benson MC, McKiernan JM, Badani KK**. The number of negative pelvic lymph nodes removed does not affect the risk of biochemical failure after radical prostatectomy. *BJU Int* 2010; 105: 176–9

28 **Schiavina R, Manferrari F, Garofalo M et al.** The extent of pelvic lymph node dissection correlates with the biochemical recurrence rate in patients with intermediate- and high-risk prostate cancer. *BJU Int* 2011; 108: 1262–8

29 **Abdollah F, Gandaglia G, Suardi N et al.** More extensive pelvic lymph node dissection improves survival in patients with node-positive prostate cancer. *Eur Urol* 2015; 67: 212–9

30 **Aizer AA, Wilhite TJ, Chen MH et al.** Lack of reduction in racial disparities in cancer-specific mortality over a 20-year period. *Cancer* 2014; 120: 1532–9

31 **Taksler GB, Keating NL, Cutler DM**. Explaining racial differences in prostate cancer mortality. *Cancer* 2012; 118: 4280–9

32 **Daskivich TJ, Kwan L, Dash A, Litwin MS**. Racial parity in tumor burden, treatment choice and survival outcomes in men with prostate cancer in the VA healthcare system. *Prostate Cancer Prostatic Dis* 2015; 18: 104–9

33 **Nguyen MM, Gill IS**. Coded tumor size may be unreliable for small metastatic renal cancers in the Surveillance, Epidemiology, and End Results dataset. *Urology* 2010; 75: 266–70

Correspondence: Paul L. Nguyen, 75 Francis St., Boston, MA 02115, USA

e-mail: pnguyen@LROC.harvard.edu

Abbreviations: AHR, adjusted hazard ratio; LN, lymph node; (P)CSM, (prostate) cancer-specific mortality; RP, radical prostatectomy; SEER, Surveillance, Epidemiology, and End Results.