Title: Association between very small tumor size and increased cancer-specific mortality following radical prostatectomy in node-positive prostate cancer

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Abstract

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 to larger node-positive tumors.

Subjects/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 tumor size by largest dimension (stratified into: (1) microscopic focus only or 1 mm; (2) 2-15 mm; (3) 16-30 mm; (4) greater than 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-Gray model for competing risks after controlling for race, tumor grade, T stage, receipt of radiation, number of dissected LNs, number of positive LNs, year of diagnosis, and age at diagnosis.

Results: Median follow-up was 11.8 years. There was a significant interaction between tumor size and LN involvement (P-interaction < 0.001). In the absence of LN involvement (N=36,561), the risk of 10-year PCSM increased monotonically with increasing tumor size. Among patients with LN involvement (N=940), those with the smallest tumors had increased 10-year PCSM compared to patients with tumors sized 2-15 mm (24.7% vs. 11.8%; adjusted hazard ratio [AHR]

= 2.84; 95% confidence interval [CI], 1.21 to 6.71; P = 0.017) or 16-30 mm (24.7% vs. 15.5%; AHR = 3.12; 95% CI, 1.51 to 6.49; P = 0.002) and similar 10-year PCSM compared to those with tumors greater than 30 mm (24.7% vs. 24.9%; P = 0.156).

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

Introduction

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

Patients and Methods

Patient selection

The Surveillance, Epidemiology, and End Results (SEER) program is sponsored by the National Cancer Institute and collects cancer incidence, diagnostic and treatment-related information from up to 18 registries, covering 26% of the US 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 radical prostatectomy and who had known tumor size data. The years of inclusion were selected because detailed tumor size was not recorded prior to 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 radical prostatectomy in order to allow for accurate assessment of tumor size; for patients who were treated with radical prostatectomy, the SEER database records tumor size according to the longest dimension of the primary tumor listed on the pathology report [7]. This study was approved by the institutional review board.

Statistical analyses

Stata/MP 13.1 (StataCorp, College Station, TX) was used for all statistical analyses. The primary study variables were tumor size by largest dimension, regional lymph node involvement, and the corresponding interaction term. To allow for statistical comparison between groups, patients were stratified according to the following pre-determined size strata: (1) microscopic focus only or 1 mm; (2) 2-15 mm; (3) 16-30 mm; (4) greater than 30 mm. Size strata were determined such that the first group contained the smallest possible tumors recorded in the SEER database, and the remaining three groups were equally spaced and divided the node-positive cohort into roughly three equal sizes.

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 χ^2 test, as appropriate. Using patients with tumors 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 tumor grade (Gleason score less than or equal to 7 versus 8-10), race, age at diagnosis, year of diagnosis (1988-1994 vs. 1995-2001), number of nodes positive, number of nodes dissected (< 6

nodes vs. ≥ 6 nodes), T stage, and receipt of radiation treatment. When we compared the PCSM of patients with the smallest tumors (microscopic focus only or 1 mm) to the PCSM of those with tumors sized 16-30 mm or greater than 30 mm, the group with the larger tumors was chosen as the referent group. We also modeled the impact of an interaction term, obtained by multiplying nodal status with tumor size. To evaluate tumor size as a continuous variable, we also fit a quadratic competing risks model in tumor size over the range 1-15 mm, adjusting for the same variables as prior. This range was chosen because we hypothesized that the descending part of the U-shape between tumor size and PCSM would occur over the small range 1-7 mm including only approximately 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 modeled 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 cut points between strata by up to 5 mm in either direction, keeping the definition of the smallest group fixed.

Results

Baseline characteristics

Median follow-up was 11.8 years. There were 36,561 patients with node-negative disease and 940 patients with node-positive disease. Patients with node-positive disease tended to have larger primary tumors, higher-grade disease, an earlier year of diagnosis, higher T stage, and more lymph nodes examined than those with node-negative disease (Table 1, $p < 0.001$). Approximately 22.8% of patients with node-negative disease and 6.0% of patients with node-positive disease were in the smallest size stratum. There were no significant differences in age or racial composition of patients with node-negative or node-positive disease (Table 1). In total, 4.8% of patients with node-negative and 23.8% of patients with node-positive disease died from prostate cancer.

Very small prostate cancers are associated with increased PCSM among node-positive patients

There was a significant interaction between tumor size and lymph node involvement (p-interaction < 0.001; see Figures 1 and 2). Among node-positive cases, tumors that were very small (microscopic foci only or 1 mm) conferred an increased risk of 10-year PCSM compared to tumors that were 2-15 mm in size (24.7% vs. 11.8%; adjusted hazard ratio [AHR] = 2.84; 95% confidence interval [CI], 1.21 to 6.71; P = 0.017) or 16-30 mm in size (24.7% vs. 15.5%; AHR = 3.12; 95% CI, 1.51 to 6.49; P = 0.002), even after controlling for multiple patient-specific factors, including tumor grade and receipt of radiation treatment. Patients with very small tumors had similar 10-year PCSM compared to those with tumors that were greater than 30 mm (24.7% vs. 24.9%; P = 0.156).

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

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

Similarly, modeling tumor size as a continuous variable using a quadratic and linear term confirmed the U-shaped relationship between tumor size and PCSM among node-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 tumor sizes of 1 and 9 mm with a local minimum at 9 mm before PCSM begins to rise with tumor size. There was no such significant relationship among node-negative cases.

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

Discussion

In this study, we provide the first evidence that tumor size and lymph node status may interact to provide prognostic information for patients with prostate cancer treated with radical prostatectomy. In particular, we found that among men with node-positive disease, very small primary tumors were associated with nearly double the risk of PCSM compared to tumors sized 2-15 mm or 16-30 mm, even after adjusting for potential explanatory factors such as tumor grade, race, and number of involved nodes. On the other hand, among those with node-negative disease, the risk of PCSM increased monotonically with tumor size. These findings were confirmed when modeling tumor size as a continuous quadratic variable. Our findings raise the intriguing possibility that small node-positive prostate cancers represent a unique and more aggressive disease process compared to larger node-positive tumors. These results challenge the notion that increasing tumor bulk is associated with equal or worse outcomes in the setting of node-positive prostate cancer [10,11].

This finding has important implications for researchers and clinicians. First, this 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 tumor acquire additional mutations as the tumor grows to a larger size, increasing the likelihood that some cells acquire requisite mutations for colonization of regional lymph nodes 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 results suggest that in patients with evidence of nodal spread, the presence of a very small primary tumor 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 lymph node metastasis. Either way, such small tumors may represent biologically

aggressive cancers. The difference in PCSM between very small and larger node-positive tumors was present after adjusting for tumor grade and T stage, which suggests that the increased biological aggressiveness of very small node-positive tumors may provide prognostic information beyond what is captured by pathological assessment of T stage and size. Uncovering the biological underpinnings of small tumors associated with lymph node involvement might lead to the discovery of new genomic changes in this subset of tumors or to the discovery of new drug targets or prognostic markers.

Second, even though it is likely that many patients with node-positive disease will receive aggressive therapy, our results emphasize that aggressive adjuvant treatment, most likely with androgen deprivation therapy [17,18], might be especially important for those with very small primary tumors. The presence of a very small primary tumor in the setting of nodal involvement conferred an absolute increase in the risk of 10-year PCSM of 12.9% compared to larger (2-15 mm) tumors; this risk increase was larger than the 7.4-11.1% absolute difference in 10-year PCSM between node-positive tumors sized 2-30 mm and similarly sized node-negative tumors. Therefore, the presence of a very small primary tumor in the setting of nodal involvement may represent an even more adverse prognostic factor than the presence of lymph node involvement alone. While we did not study the role of adjuvant treatment, our data might still be used by physicians to counsel patients with very small node-positive tumors about prognosis and to guide therapy decisions.

Previous studies have identified increasing prostate tumor volume as a negative prognostic factor in organ-confined disease and increasing lymph node tumor volume as a negative prognostic factor in node-positive disease [4,5,19-22]. In the node-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 node-positive disease. However, others have previously suggested that small tumor foci might be aggressive precursors of metastatic spread even compared to larger tumors. In a recent case report [23], Haffner and colleagues 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 of 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 lymph nodes. This finding, like our study, suggests that even small tumors can be potentially lethal, which raises the possibility that the largest lesion in a tumor may not be the most dangerous, a concept which might have implications for focal therapy [24]. A similar relationship between very small tumor size and increased mortality has also been observed in node-positive breast cancer [25]. It is possible that similar biological mechanisms might underlie the U-shaped relationship between tumor size and cancer-specific mortality 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 [26], due to differences in follow-up or changes in treatment; more involved lymph nodes [10]; higher grade disease [1]; and lack of adjuvant radiation in the node-positive setting [27]. We did not find that the number of dissected lymph nodes had an impact on outcome, consistent with prior work [28,29], although some have found an association between the number of examined lymph nodes and outcomes in select situations [30,31]. We did not find a relationship between Black race and increased PCSM, in contrast to some prior research [32], 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 [33,34].

Our 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 tumor 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 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 tumor size and increased PCSM. Our 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 study was retrospective and has the general limitations of this study design, including susceptibility to selection bias. For example, patients with small primary tumors might have been less likely to be diagnosed or experienced delayed diagnosis due to having lower serum PSA levels than those with larger tumors; however, all patients with node-positive disease likely had elevated PSA due to relatively high tumor volume regardless of the size of the primary tumor. Therefore, the impact of small primary tumor size on the rate or timing of diagnosis from PSA screening was likely small. For patients with node-negative disease, while those with small tumors 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 tumors. 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 tumor biology or aggressiveness. However, we adjusted for receipt of radiation therapy, and patients with node-positive disease are likely to have received similarly aggressive systemic therapy (i.e. androgen deprivation therapy) regardless of the size of their primary tumors because management in this patient population would typically be dictated by the presence of lymph node involvement.

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

Fourth, we did not have centralized pathology review, and it is possible that there is significant heterogeneity in how the samples were handled and analyzed. In addition, the SEER database has previously been reported to contain errors in recording of tumor size in other sites [35]. While such errors and differences in sample handling may reduce the reliability of our results, they are likely to be random and therefore not systematically bias our analyses. Nevertheless, our findings must be validated in other clinical datasets.

Conclusion

In this study, we found that lymph node involvement paradoxically interacts with tumor size among prostate cancer patients treated with radical prostatectomy. In the setting of lymph node involvement, very small prostate cancers were associated with approximately double the risk of PCSM as tumors sized 2-15 mm or 16-30 mm, whereas among node-negative patients, PCSM rose monotonically with primary tumor 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 lymph node involvement in order to elucidate the mechanisms underlying the aggressiveness of these tumors. A deeper understanding of the biology of these tumors 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 tumors and lymph node involvement regarding their increased risk of PCSM and to guide therapy decisions.

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Conflict of interest statement: PLN has worked as a consultant for Medivation and GenomeDx. QDT has been a speaker for Intuitive Surgical. The other authors have no conflicts to disclose.

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Figure Legends

Figure 1. Prostate cancer-specific mortality over time among node-negative patients with prostate cancer by the longest dimension of the primary tumor.

Figure 2. Prostate cancer-specific mortality over time among node-positive patients with prostate cancer by the longest dimension of the primary tumor.

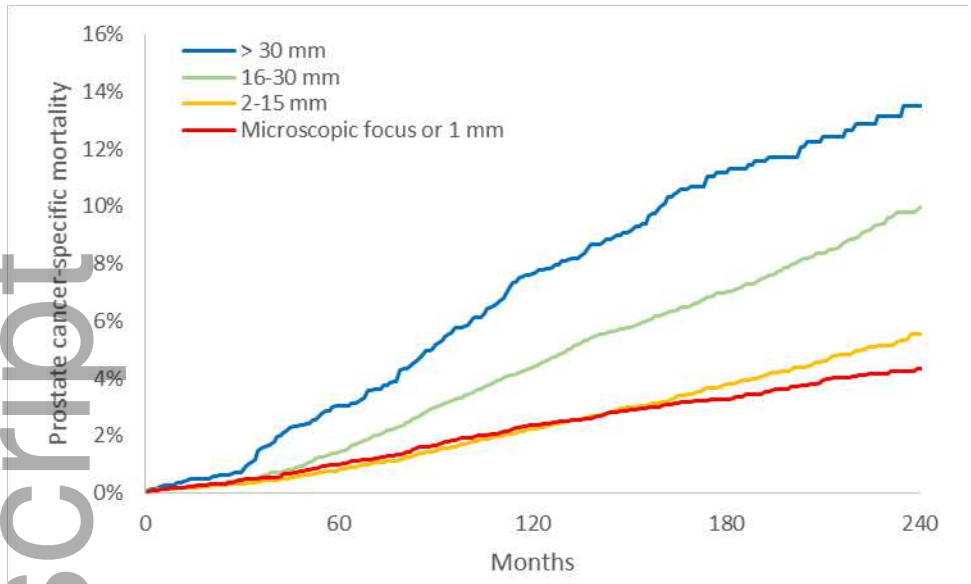
Figure 3. Adjusted hazard ratios for prostate cancer-specific mortality (PCSM) among patients with node-negative (A) and node-positive (B) prostate cancer by the longest dimension of the primary tumor. (NS: not significant)

Table 1. Baseline patient characteristics. P-values correspond to differences between node-negative and node-positive patients. *IQR: Inter-quartile range

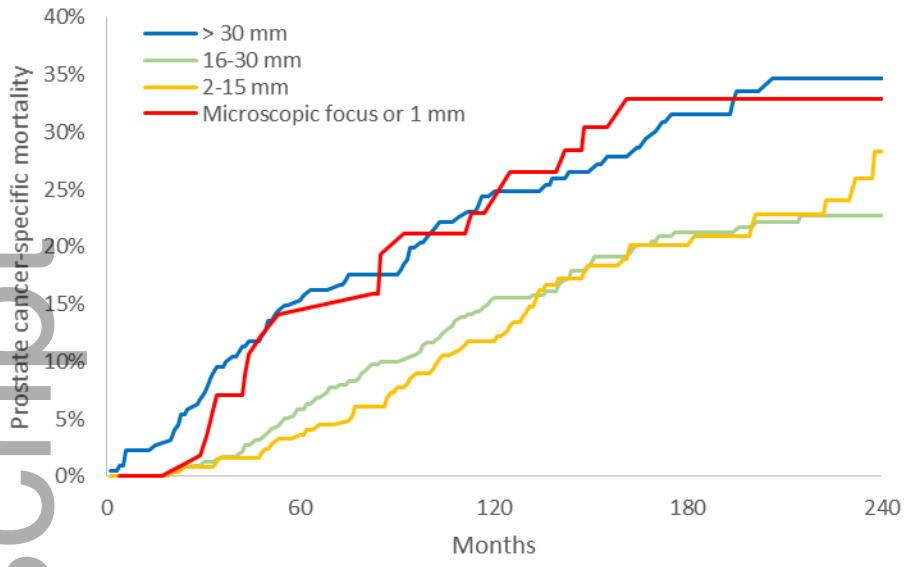
	Patients						
	Total (N = 37,501)		Node-negative (N = 36,561)		Node-positive (N = 940)		
Patient Characteristic	N	%	N	%	N	%	*P*
Median follow-up, years (IQR*)	11.8 (10-14.9)		11.8 (10-14.9)		11.2 (6.8-14.6)		< 0.001
Year of Diagnosis							< 0.001
1988-1994	10,394	27.7%	9,940	27.2%	454	48.3%	
1995-2001	27,107	72.3%	26,621	72.8%	486	51.7%	
Patient age (years)							0.431
≤ 65	18,894	50.4%	18,842	51.5%	472	50.2%	
> 65	18,607	49.6%	17,719	48.5%	468	49.8%	
Race							0.421
White	32,025	85.4%	31,222	85.4%	803	85.4%	
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	0.0%	
Tumor Size							< 0.001
Microscopic focus only or 1 mm	8,378	22.3%	8,322	22.8%	56	6.0%	
2-15 mm	16,662	44.4%	16,413	44.9%	249	26.5%	
16-30 mm	8,784	23.4%	8,467	23.2%	317	33.7%	
> 30 mm	3,677	9.8%	3,359	9.2%	318	33.8%	
Gleason score							< 0.001
≤ 7	30,536	81.4%	30,054	82.2%	482	51.3%	
> 7	6,390	17.0%	5,944	16.3%	446	47.4%	
Unknown	575	1.5%	563	1.5%	12	1.3%	
T stage							< 0.001
T1	12,790	34.1%	12,669	34.7%	121	12.9%	
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 lymph nodes examined							< 0.001
≤ 6	21,181	56.5%	20,932	57.3%	249	26.5%	
> 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

Table 2. Multivariable competing risks regression for prostate cancer-specific mortality (PCSM) including year of diagnosis, age, race, Gleason score, number of dissected lymph nodes (LNs), number of positive lymph nodes, receipt of radiation therapy, T stage, tumor size and nodal status. For analysis of tumor size and nodal status, patients with the smallest node-negative tumors were chosen as the referent group.

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



bju13248-fig-0001.tif



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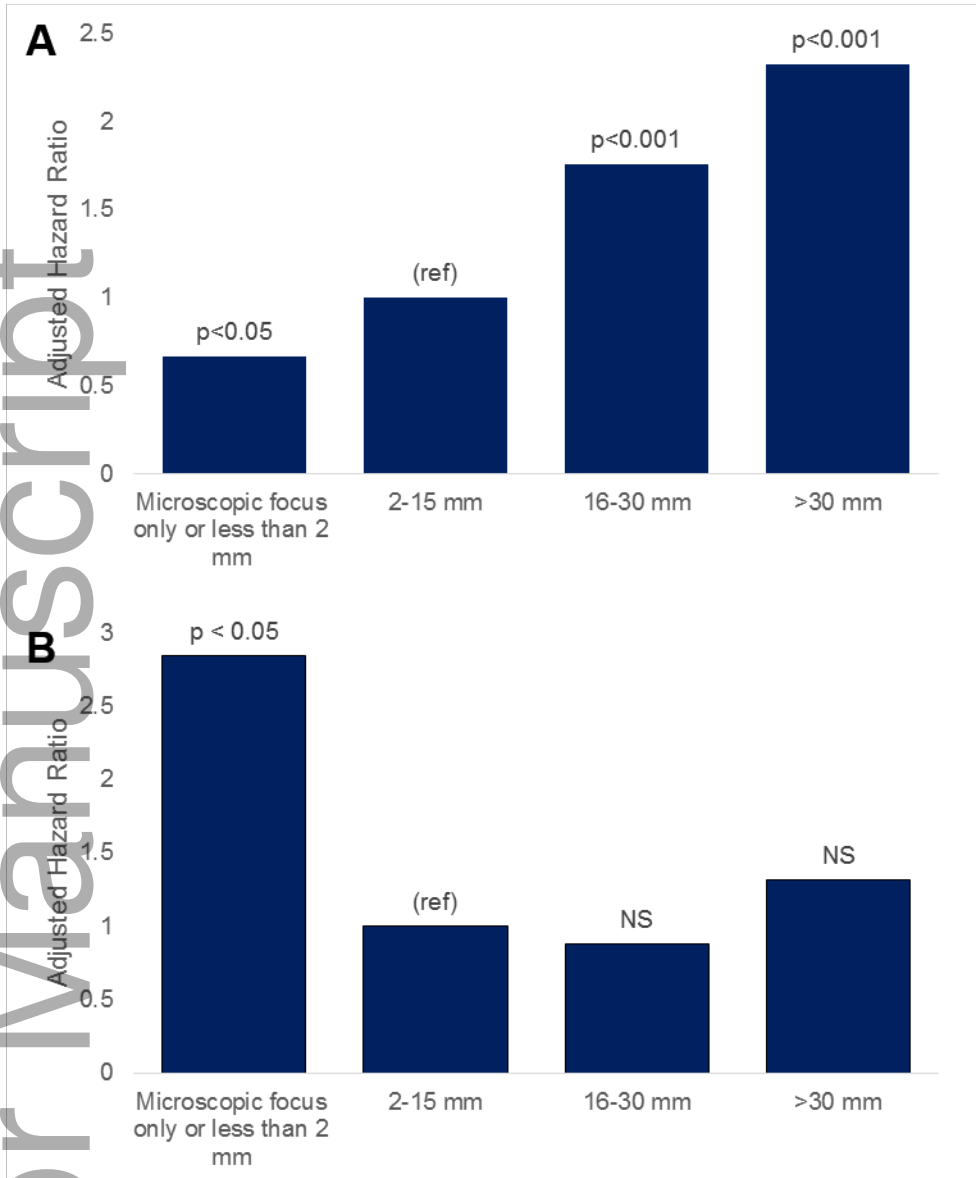

bju13248-fig-0003.tif