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Does Subclassification of Pathologically Organ Confined (pT2) Prostate Cancer Provide Prognostic Discrimination of Outcomes after Radical Prostatectomy?

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Abstract

Purpose: We tested the latest update in the prostate cancer staging system by assessing the prognostic association of pT2 subclassification with the probability of survival related outcomes in patients who underwent radical prostatectomy.

Materials and Methods: We retrospectively analyzed the records of a total of 15,305 patients who underwent radical prostatectomy at 2 referral centers between 1985 and 2016, and had pT2 disease at the final pathological evaluation. Descriptive statistics were used to compare baseline data stratified by pT2 substages (pT2a/b vs pT2c). Cox regression models were adjusted for institution analyzed differences in the rate of biochemical recurrence, metastasis, cancer specific death and overall mortality. Multivariable Cox regression models were used to evaluate the predictive value of pT2 subclassification for survival, including the linear predictor from the Stephenson nomogram.

Results: Prostate specific antigen levels and Gleason score differed significantly between the pT2 substages (each $p < 0.0001$). At a median followup of 6.0 years (IQR 3.3–10.1) 2,083 patients had biochemical recurrence, 161 had metastases, 43 had died of prostate cancer and 1,032 had died of another cause. On univariate analysis the pT2 subclassification was significantly associated with biochemical recurrence ($p = 0.001$) and distant metastasis ($p = 0.033$) but not with cancer specific death ($p = 0.6$) or overall mortality ($p = 0.3$). Multivariable analysis showed no evidence of a significant association between the pT2 subclassification and biochemical recurrence ($p = 0.4$)

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or distant metastasis (p = 0.6). Multivariable analysis of cancer specific death and overall mortality was omitted due to lack of significance on univariate analysis.

Conclusions: Subclassification of pT2 prostate cancer is not a prognostic indicator of survival related outcomes after radical prostatectomy. Our results validate the elimination of pT2 substages in the updated staging system.

Keywords

prostatic neoplasms; prostatectomy; neoplasm staging; mortality; neoplasm metastasis

THE purpose of a cancer staging system is to define patient groups with an outcome that is more homogeneous in groups than between groups and also maximize prognostic accuracy. Higher stage should be associated with poorer outcomes. In the AJCC Cancer Staging Manual, 8th edition the TNM staging system eliminates the subclassification of pT2 disease.[1,2] However, there was insufficient evidence on whether the pT2 subclassification has prognostic value in patients who undergo RP for clinically localized disease. Previous studies attempted to evaluate staging systems using BCR as an end point.[3–7] However, PSA correlates poorly with survival outcomes.[8–10]

The purpose of the current study was to validate the current staging system regarding organ confined prostate cancer. Using data from 2 academic institutions to assemble what is to our knowledge the largest cohort of patients with pT2 disease analyzed to date, we assessed the prognostic association of pT2 subclassification with the probability of BCR, distant metastasis, cancer specific death and overall mortality in patients who underwent RP for clinically localized prostate cancer.

PATIENTS AND METHODS

Patients

With institutional review board approval we retrospectively reviewed prospectively collected data on 19,160 patients with pT2 disease at RP, including 7,764 at MSKCC from 1985 to 2016 and 11,396 at Mayo Clinic from 1990 to 2012. In this cohort RP was performed by different surgeons with routine pelvic lymph node dissection, including the removal of all lymphatic tissue along the external and internal iliac vessels, and in the obturator fossa. A total of 478 patients were excluded from our analysis due to missing information on pT2 substage or staging system and 36 were excluded due to metastatic disease at the time of surgery. In addition, to isolate the effect of stage and elude potential confounding due to adjuvant therapy effects on outcomes 2,679 patients were excluded due to positive surgical margins, 535 were excluded since they received neoadjuvant treatment and 127 were excluded due to lymph node metastasis. The final study population consisted of 15,305 patients. All individual participants included in the study provided informed consent.

Pathological Findings

During the entire study period RP specimens were processed as previously described at the respective institutions.[11,12] Briefly, specimens were inspected macroscopically and weighed, and the dimensions were recorded. At MSKCC from 1998 and thereafter the intact prostate

and seminal vesicles were inked in green on the right side and in blue on the left side while in the fresh state. Also, the superficial fragments of muscular tissue surrounding the proximal urethra (ie the bladder neck) were shaved. To permit assessment of the inked apical margin the most apical 3 mm of the gland were sectioned, further segmented radially in cone-like fashion and embedded. The seminal vesicles were amputated at the junction with the prostate and submitted separately. Finally, the remaining bulk of the gland was sectioned from apex to base at approximately 3 mm intervals and entirely submitted as whole mount sections for examination.

At Mayo Clinic RP specimens were processed using a systematic limited sampling protocol consisting of frozen sections initially, followed by permanent section analysis the next day. At the time of the procedure the apex and base were examined in multiple sections. At least 8 axial sections were taken through the remainder of the peripheral zone along with a section through each seminal vesicle for an average of 14 sections per specimen. All sections were then reexamined the next day using hematoxylin and eosin stained permanent sections.

At each institution staging data were available on primary tumor and lymph nodes according to the 2017 edition of the TNM staging system.[1,2] By reviewing pathology reports the specimens had been reclassified as the TNM staging system evolved.

Oncologic Outcomes

The followup protocol generally included serum PSA and physical examination at 6 weeks, every 3 to 6 months for 5 years and annually thereafter. Followup data were retrieved from institutional electronic databases.

For this analysis BCR was defined as a single post-operative PSA measurement of 0.4 ng/ml or greater. Sensitivity analysis was performed with BCR defined as PSA 0.1 ng/ml or greater with a confirmatory rise in the MSKCC cohort. Recurrence information was based on clinical and radiological findings, and metastasis was defined as the first evidence of distant relapse. Death from prostate cancer vs another cause was documented according to medical records or death certificates.

Statistical Analyses

We used the Wilcoxon rank sum and chi-square tests to compare baseline data stratified by pT2 substages. In the Mayo Clinic database and part of the MSKCC database the pT2a and pT2b substages are grouped in the same category and the existence of pT2b disease is controversial.[13] Therefore, we decided to focus the analysis on pT2a/b (unilateral) vs T2c (bilateral) disease.

Cox proportional hazards models adjusted for institution were used to compare rates of BCR, metastasis, death from disease and overall mortality between patients with pT2a/b and pT2c disease. When these Cox models yielded significant differences, the predictive value of the pT2 subclassification on survival was evaluated in multivariable Cox regression models including the linear predictor from the Stephenson nomogram[14] and the institution. The Stephenson nomogram was used to calculate a predicted risk of BCR based on preoperative PSA, post-RP Gleason grade, extracapsular extension, seminal vesicle invasion, nodal status

and surgical margin status. Additionally, we included an interaction term between pT2 substage and institution to assess whether associations differed based on institution.

As we had data on surgeries done at Mayo Clinic until 2012 but at MSKCC until 2016, we performed a sensitivity analysis which repeated all analyses but only included surgeries up to the end of 2012. As an additional sensitivity analysis we repeated the analyses after restricting the cohorts to all surgeries performed between 2007 and 2012 to include patients with modern grading only. We also repeated the main analyses using clinical T2 substage instead of pathological T2 stage.

All p values are 2-sided with statistical significance considered at $\alpha = 0.05$. To assess the precision of the obtained estimates we calculated the 95% CIs. All analyses were performed with Stata®, version 13.

RESULTS

Baseline and Pathological Data

In the entire cohort median age was 61 (IQR 56–66) and median serum PSA was 5.2 ng/ml (IQR 3.9–7.2). There was a small but significant difference in median PSA of 0.1 ng/ml between pT2a/b and pT2c cases ($p < 0.0001$, table 1). In approximately half of the patients with pT2c disease the cancer was Gleason 7 or greater compared to less than a third of patients with pT2a/b disease ($p < 0.0001$, table 1).

Oncologic Outcomes

Median followup in survivors was 6.0 years (IQR 3.3–10.1). During followup 2,083 patients had BCR, metastases developed in 161, 43 died of prostate cancer and 1,032 died of another cause. After adjusting for institution the pT2 subclassification was significantly associated with BCR and with distant metastasis ($p = 0.001$ and 0.03, respectively). However, we found no evidence of an association with overall mortality and with death from disease ($p = 0.3$ and 0.6, respectively). Figures 1 to 4 show cumulative incidence estimates adjusted for institution. table 2 lists adjusted estimates at 10 years.

When controlling for other prognostic factors, we found no significant association of the pT2 subclassification with BCR or distant metastasis ($p = 0.4$ and 0.6, respectively, table 3). Sensitivity analyses defining BCR as PSA 0.1 ng/ml or greater with a confirmatory rise were consistent with the main analysis (HR 1.29, 95% CI 0.97–1.73, $p = 0.09$). We found no evidence that the association between pT2 substage and outcomes differed by institution (data not shown).

As an additional sensitivity analysis, we repeated the analyses after limiting the cohort to surgeries performed up to December 31, 2012. All results were consistent with the main analyses. Bilateral disease showed a worse BCR rate when adjusting for institution only ($p = 0.001$), but not when adjusting for other prognostic factors (HR 1.04, 95% CI 0.95–1.14, $p = 0.4$). There was also a significant association between the pT2 subclassification and distant metastasis on univariate analysis ($p = 0.037$) but not on multivariable analysis (HR 1.09,

95% CI 0.77–1.52, p = 0.6). There was also no evidence of an association with cancer specific death or overall mortality on univariate analysis (p = 0.6 and 0.3, respectively).

To account for modern grading we also repeated these analyses in patients treated from 2007 to 2012 only. As in the main analyses, bilateral disease was associated with a higher BCR rate when adjusting for institution only (p = 0.039) but not when controlling for other prognostic factors (HR 1.12, 95% CI 0.89–1.40, p = 0.4). In this cohort we found no evidence of a difference in the rate of distant metastasis or overall mortality (p = 0.6 and 0.8, respectively) based on the presence of bilateral disease. Death from disease was not analyzed due to a limited number of events.

On univariate analysis in the 4,827 patients who had clinical stage T2a, T2b or T2c disease we found no evidence of an association between clinical T2 stage and BCR (p = 0.1), distant metastasis (p = 0.07), cancer specific death (p = 0.5) or overall mortality (p = 0.6).

DISCUSSION

The advent of PSA based screening led to early detection and to downward stage migration of prostate cancer. Today most patients who undergo RP have organ confined disease.[15,16] The AJCC/UICC (Union for International Cancer Control) TNM staging system has been repeatedly revised since 1992 with the current 2017 system eliminating the 3-tiered pT2 subclassification.1,2 However, whether subclassification of pT2 prostate cancer adds prognostic value has not been robustly tested. In this study we investigated the effects of using pT2 substages not only for BCR but also for stronger end points. We found that the pT2 subclassification did not add prognostic information to the outcomes of BCR, distant metastasis, cancer specific death or overall mortality.

Freedland et al observed no difference in BCR risk in patients with unilateral vs bilateral organ confined prostate cancer at RP.[3] In studies by Caso[6] and Chun[7] et al, which included a total of 3,716 patients, the 3-tiered pT2 subclassification did not offer additional prognostic value compared to well established risk factors for BCR. Similar negative findings were reported in smaller series.[4,5] Our current analysis validates these results in a larger cohort with longer followup and more aggressive pathological characteristics. For instance, compared to the analysis by Freedland et al in which 81% of patients had a pathological Gleason score of 6 or less,[3] this proportion was 55% in the current study. In the study by Chun et al median followup was only 24 months and 62% of the patients had a pathological Gleason score of 6 or less.[7]

However, there are limitations in using BCR as an end point. The natural history of patients with PSA failure is variable and most patients have an indolent clinical course.[8–10] In a study by Bianco et al men with BCR had a similar 1-year probability of death from prostate cancer vs death from another cause (32% vs 33%).[8] At a median 9-year followup in the Mayo Clinic cohort BCR translated into clinical evidence of prostate cancer in 29% of the patients and only 8% died of prostate cancer.[10] Along the same lines, in The Johns Hopkins Medical Institutions RP cohort median survival had not been reached 16 years after first evidence of BCR.[9]

Our study shows that the rates of metastasis and cancer specific death at 10 years were relatively low in this pT2 population at 1.6% and 0.4%, respectively. These rates are consistent with those in previous studies. In a cohort of 370 men with a median 9-year followup after laparoscopic RP the 10-year clinical progression-free survival rate was 97.3% in those with pT2 disease.[17] In a multicenter study in the United States in 11,521 patients who underwent RP the 15-year prostate cancer specific mortality risk was 0.8% to 1.5% in those with pT2 disease.[18] These men were more likely to die of competing causes. Similarly 2 European studies with 10 years of followup showed a 98% to 98.7% cancer specific survival rates in patients with pT2 prostate cancer at RP.[19,20] Thus, pT2 cancer at RP represents a clinically homogeneous group of patients with an overall good prognosis.

Our results reinforce the concept that a field effect exists in prostate carcinogenesis, ie multifocal prostate cancer foci arise independently in prostatic tissue. Although the existence of the field effect in prostate cancer has been suggested for 20 years,[21,22] more conclusive evidence was recently reported.[23,24] Kosari et al found a common cancer transcriptome in benign prostate tissue adjacent to prostate cancer and unmatched prostate cancer, suggesting a wide field effect.[24]

Our results validate the elimination of the pT2 subclassification in the new AJCC/TNM staging system.[1] The preoperative serum PSA level and pathological Gleason grade remain the strongest prognostic factors in patients with margin negative pT2 disease.[3–7] The rationale for pT2 subclassification had also been questioned from a biological perspective. 1) Is it appropriate that a single unilateral large tumor is assigned a lower pathological stage than 2 small bilateral tumors?[25] 2) Approximately 80% of prostate cancers are multifocal.[4,13] 3) It was postulated that true pT2b cancer, ie unilateral cancer occupying more than half of 1 lobe, may not exist. Eichelberger et al examined 369 totally embedded and serially sectioned whole mount RP specimens.[13] While 75% of these tumors were classified as pT2, not a single pT2b tumor was detected and 312 cases (85%) were multifocal. This controversial issue may explain the large variation in pT2b reporting among pathologists.[25]

Looking ahead, a more informative grouping of pT2 disease may be based on index tumor size or volume, or the percent of the gland occupied by tumor.[26–28] Wise et al reported that index tumor volume alone was a predictor of prognosis that was as equally powerful as all tumor volume.[28] Thus, index tumor volume may become a reliable predictor of outcomes after RP. However, no accepted standard technique of tumor volume measurement exists. Therefore, the prognostic value of index tumor volume and other parameters remains uncertain.

Our analysis is subject to the limitations inherent to retrospective studies, such as the possibility of uncaptured events after hospital discharge. To counterbalance that there was regular correspondence with all patients who were not followed at the 2 institutions where the surgery was performed. Central pathological review was not logistically feasible, given the size of the cohort. However, the assessment of RP specimens at each institution was performed by highly experienced urological pathologists. We could not consider the shift in Gleason grading that has taken place since 2005,[29] and evolved into a higher likelihood of higher grading being reported.[30] Furthermore, given the long natural history of prostate

cancer, a median followup of 6 years may not be long enough to detect differences in outcomes. Finally, our data require validation in external data sets.

These limitations notwithstanding, to our knowledge this is the first study to evaluate the effect of pT2 subclassification using robust survival end points in a large bi-institutional cohort, allowing for substantial statistical power.

CONCLUSIONS

In this bi-institutional cohort the subclassification of pT2 prostate cancer was not a prognostic indicator of BCR, metastasis, death from prostate cancer or overall mortality. Our results validate the elimination of the pT2 subclassification in the 2017 AJCC/TNM staging system.[1]

Acknowledgments

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Abbreviations and Acronyms

AJCC	American Joint Committee on Cancer
BCR	biochemical recurrence
MSKCC	Memorial Sloan Kettering Cancer Center
PSA	prostate specific antigen
RP	radical prostatectomy

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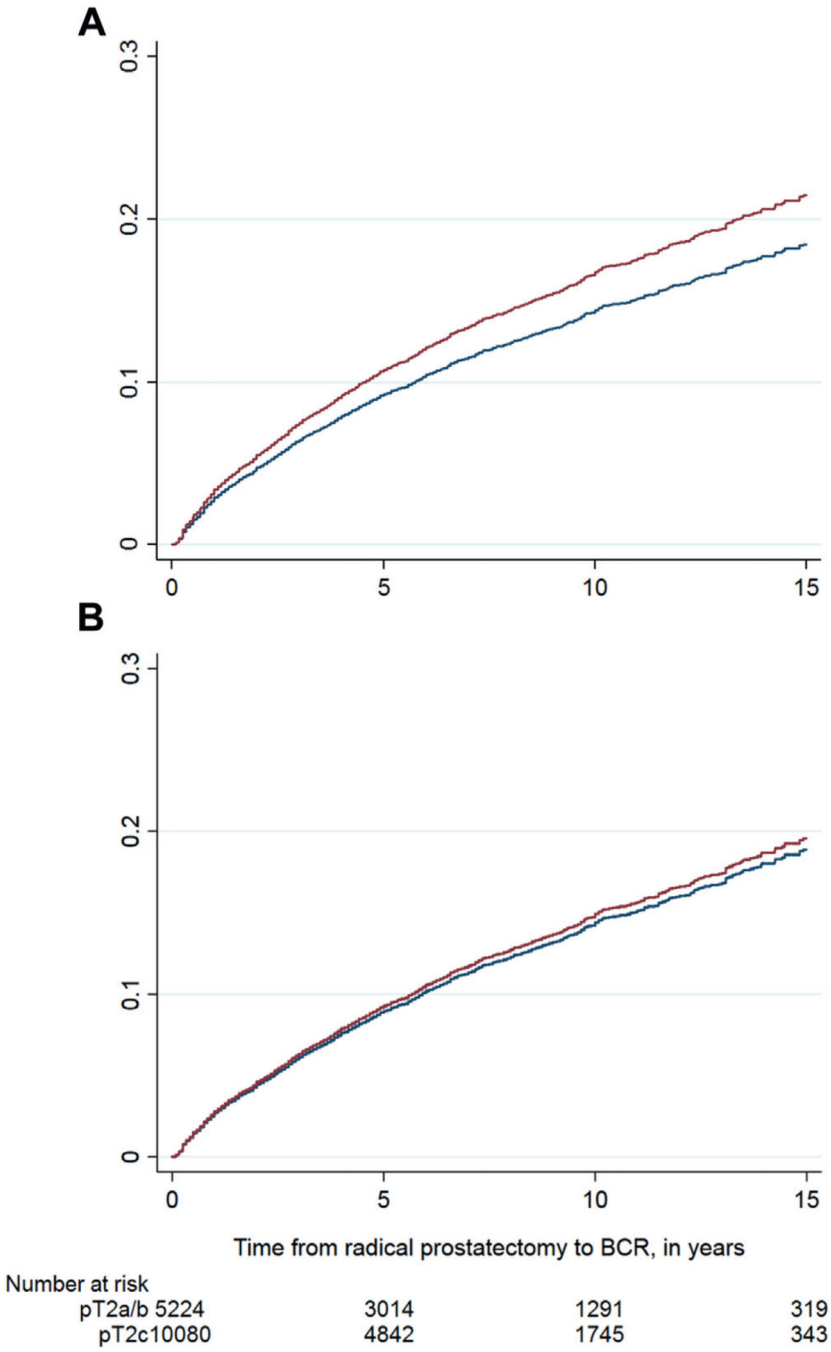

Figure 1.

Cumulative incidence estimates of biochemical recurrence adjusted for institution only (*A*), and for institution and Stephenson nomogram linear predictor (*B*). Blue curve represents pT2a/b disease. Red curve represents pT2c disease.

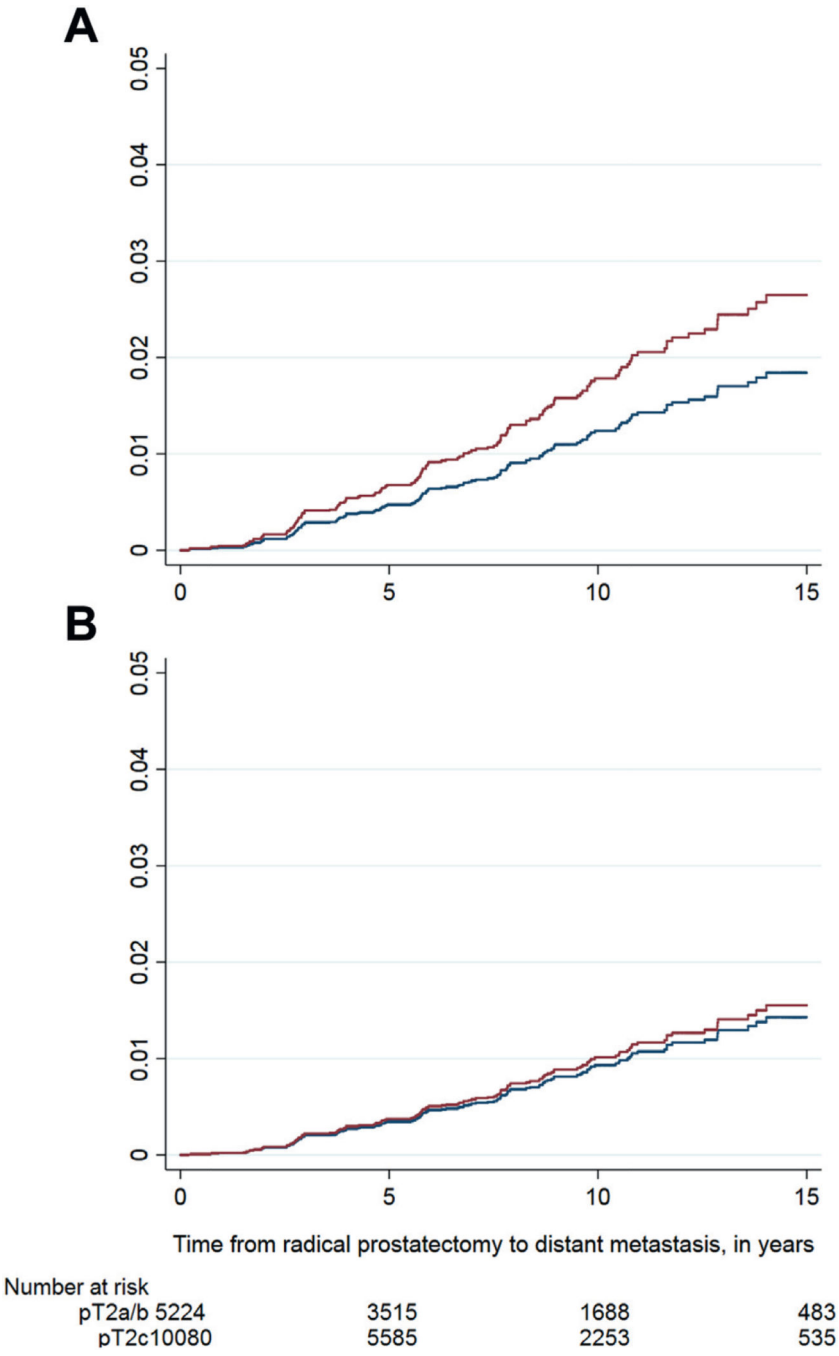

Figure 2.

Cumulative incidence estimates of distant metastasis adjusted for institution only (*A*), and for institution and Stephenson nomogram linear predictor (*B*). Blue curve represents pT2a/b disease. Red curve represents pT2c disease.

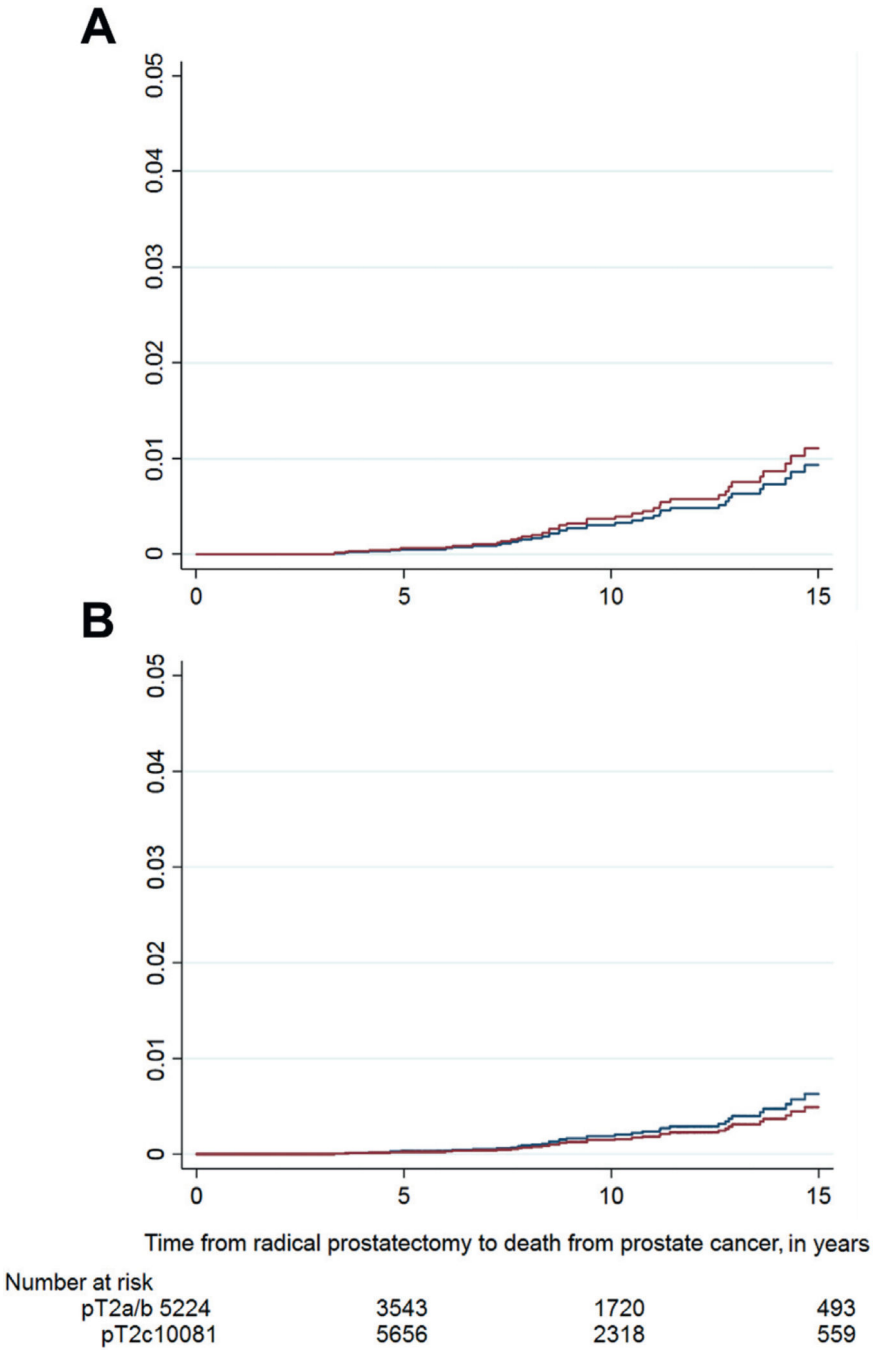

Figure 3.

Cumulative incidence estimates of death from disease adjusted for institution only (*A*), and for institution and Stephenson nomogram linear predictor (*B*). Blue curve represents pT2a/b disease. Red curve represents pT2c disease.

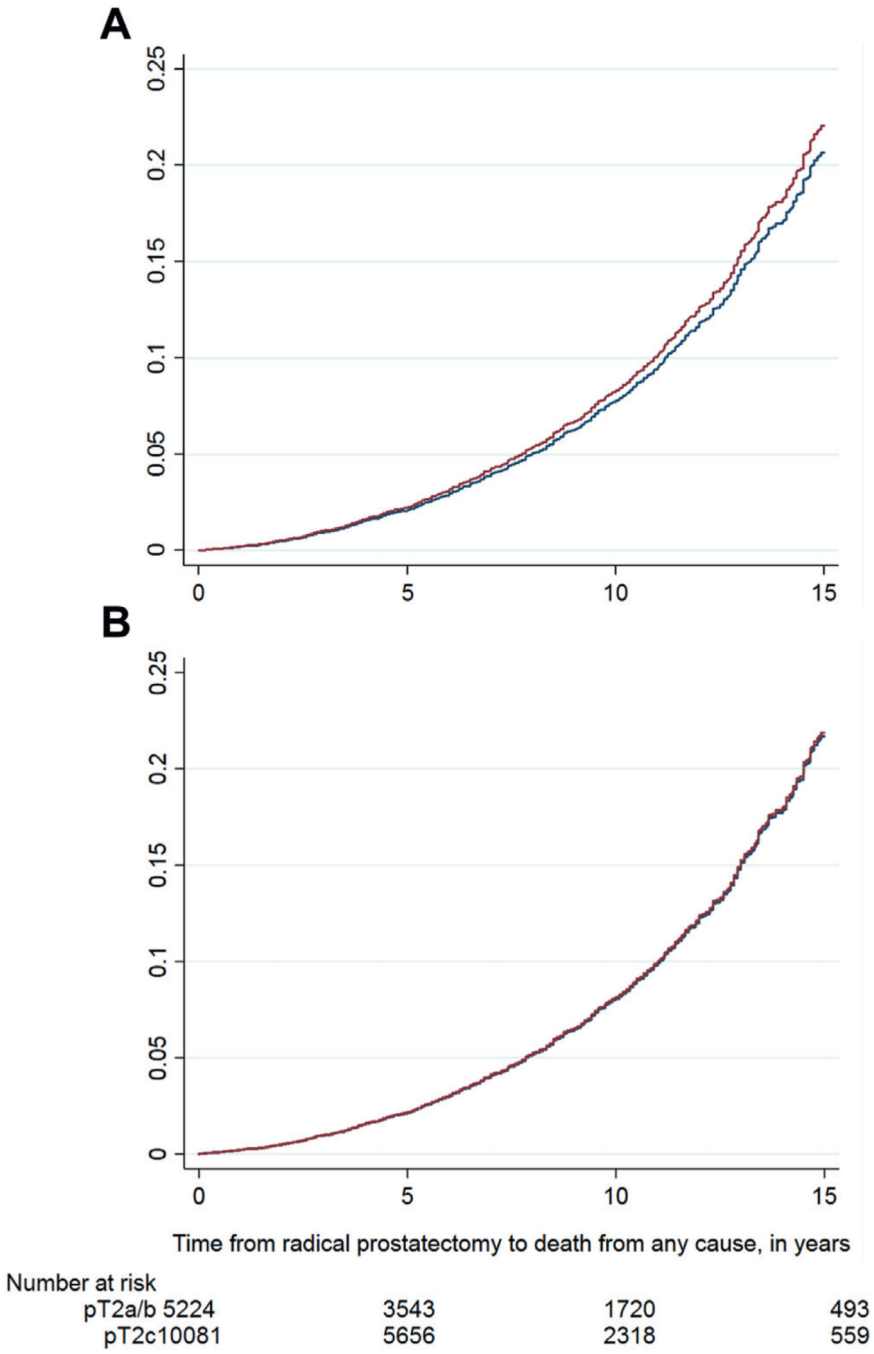

Figure 4.

Cumulative incidence estimates of overall mortality adjusted for institution only (*A*), and for institution and Stephenson nomogram linear predictor (*B*). Blue curve represents pT2a/b disease. Red curve represents pT2c disease.

Table 1.

Characteristics of 15,305 patients and disease by pT2 substage

	pT2a/b		pT2c		p Value
No. pts	5,224		10,081		–
Median age at surgery (IQR)	61	(56–66)	61	(56–66)	0.3
Median ng/ml PSA (IQR) *	5.1 (3.6–7.2)		5.2 (4.0–7.2)		<0.0001
No. pathological Grade Group (%):					
1	3,571	(68)	4,910	(49)	<0.0001
2	1,190	(23)	4,065	(40)	
3	281	(5.4)	780	(7.7)	
4	99	(1.9)	175	(1.7)	
5	56	(1.1)	108	(1.1)	
Unknown	27	(0.5)	43	(0.4)	
No. clinical T stage (%):					
T1	3,384	(65)	6,667	(66)	0.13
T2	1,723	(33)	3,151	(31)	
T3	42	(0.8)	82	(0.8)	
Unknown	75	(1.4)	181	(1.8)	
No. RP type (%):					
Open	3,835	(73)	6,457	(64)	<0.0001
Laparoscopic, nonrobot-assisted	352	(6.7)	938	(9.3)	
Robot-assisted	1,037	(20)	2,686	(27)	

* In 15,124 patients.

Table 2.

Cumulative 10-year incidence estimates by pathological T2 substage

	% Incidence Estimate (95% CI)			
	pT2a/b		pT2c	
BCR*	14.3	(13.1–15.6)	16.6	(15.5–17.8)
Distant metastasis	1.2	(0.9–1.7)	1.8	(1.4–2.2)
Prostate Ca death	0.3	(0.2–0.6)	0.4	(0.2–0.6)
Overall mortality	7.8	(6.9–8.7)	8.3	(7.5–9.1)

*Adjusted for institution.

Table 3.

Multivariable Cox regression models of probability of BCR and distant metastasis in 15,072 patients adjusted for pathological subclassification and Stephenson nomogram linear predictor[14]

Pathological Stage	HR (95% CI)
BCR:*	
pT2a/b	Referent
pT2c	1.04 (0.95–1.13)
p Value	0.4
Distant metastasis:	
pT2a/b	Referent
pT2c	1.09 (0.78–1.53)
p Value	0.6

*Also adjusted for institution.