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Bladder Cancer

Validation of the AJCC TNM Substaging of pT2 Bladder Cancer: Deep Muscle Invasion Is Associated with Significantly Worse Outcome

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Abstract

Background: The current TNM bladder cancer staging system stratifies bladder muscle invasion into superficial (pT2a) and deep (pT2b). Controversy exists regarding the significance of the extent of muscle invasion on clinical outcome.

Objective: Our aim was to compare the cancer-specific outcomes of patients with pT2 urothelial carcinoma of the bladder (UCB) at radical cystectomy (RC) in a large international cohort of patients.

Design, setting, and participants: The records of patients treated with RC for UCB at six centers were reviewed. Of the 2605 reviewed patients, 565 (21.7%) had pT2 disease. None of the patients received preoperative systemic chemotherapy or radiotherapy.

Measurements: Patients' characteristics and outcome were evaluated.

Results and limitations: The median patient age in the entire group was 66.2 yr. Of the 565 patients with pT2 UCB, 249 patients (44.1%) had substage pT2a; 316 patients (55.9%) had pT2b. One hundred and eleven patients (19.6%) had metastases to regional lymph nodes. Median follow-up was 50.5 mo. Recurrence-free survival (73.2% vs 58.7%) and cancer-specific survival (78.0% vs 65.1%) estimates were significantly better for pT2a patients compared with those with pT2b ($p = 0.002$ and $p = 0.001$, respectively). Pathologic T2 substaging was associated with worse recurrence-free and cancer-specific survival after adjusting for the effects of standard pathologic features ($p = 0.011$ and $p = 0.006$, respectively). The statistical significance of these associations was reconfirmed in subgroup analysis limited to those patients with pathologically negative lymph nodes.

Conclusions: In this large international cohort, pathologic substaging helped to stratify patients with lymph node–negative pT2 UCB into statistically significantly different risk groups. These data support the value of the current American Joint Committee on Cancer TNM staging.

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1. Introduction

Bladder cancer is the fourth most common cancer in males and the ninth most common cancer in females with 70 980 new cases and 14 330 deaths estimated for 2009 in the United States [1]. In the European Union, 104 400 cases of bladder cancer were diagnosed in 2006, and 36 500 died of bladder cancer [2]. For patients with muscle-invasive urothelial carcinoma of the bladder (UCB) and those patients with high-risk non–muscle-invasive UCB, radical cystectomy (RC) with bilateral pelvic and iliac lymphadenectomy provides accurate staging and adequate local and regional control [3–8]. Pathologic tumor stage (pT) and lymph node status are the strongest prognostic factors in patients with UCB [3–8].

The TNM bladder cancer staging system was modified in 1997 by the American Joint Committee on Cancer (AJCC) and the TNM Committee of the Union Internationale Contre le Cancer [9]. In the revised classification, bladder muscle invasion is stratified into superficial (pT2a; inner half of bladder muscle) and deep (pT2b; outer half of bladder muscle).

Several studies have reported no significant difference in oncologic outcomes between lymph node–negative pT2a and pT2b patients and concluded that the current staging system might be simplified by consolidating these substages [10–15]. However, these studies were limited by their small sample size and single-institution character. To address this question in a larger multi-institutional cohort, we compared the clinicopathologic characteristics and outcomes between patients with pT2a versus pT2b AJCC substage.

2. Methods

2.1. Patient selection and data collection

This study was approved by an institutional review board with all participating sites providing the necessary institutional data-sharing agreements before initiation of the study. A total of six worldwide tertiary care centers provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen and the final data set was produced for the current analysis.

The records of 2605 patients treated with RC for UCB between 1979 and 2008 were reviewed. No patient received preoperative chemotherapy and/or radiotherapy. Of these patients, 565 (21.7%) had pT2 disease at the time of surgery. Adjuvant chemotherapy was administered to 101 patients (17.9%) at the investigator's discretion.

2.2. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures. Genitourinary pathologists assigned tumor grade according to the 1973 World Health Organization grading system at the time of the initial diagnosis. Pathologic stage was reassigned by pathologists at each center according to the 2002 AJCC TNM staging system. Concomitant carcinoma in situ (CIS) was defined as the presence of CIS in conjunction with pathologic stage T2. Pelvic lymph node dissections were examined grossly, and all lymphoid tissue was submitted for histologic examination. Positive soft-tissue surgical margin (STSM) status was defined as the presence of tumor at inked areas of soft tissue on the RC specimen. Urethral or ureteral margin status was not considered as STSM in this analysis. Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumor cells within an endothelium-lined space without underlying muscular walls. To ensure validity of the pathologic data extraction, two investigators independently reviewed pathology from 219 patients while blinded to patient clinical parameters and the finding of the other reviewer. Interreader reliability measured using the intraclass correlation coefficient was >0.95 for each pathologic characteristic.

2.3. Follow-up

Follow-up was performed according to institutional protocols. Patients generally were seen postoperatively at least every 3 to 4 mo for the first year, semiannually for the second year, and annually thereafter. Follow-up visits consisted of a physical examination and serum chemistry evaluation, including liver function tests and alkaline phosphatase. Diagnostic imaging of the upper tracts (eg, ultrasonography and/or intravenous pyelography, computed tomography [CT] of the abdomen/pelvis with intravenous contrast) and chest radiography were performed at least annually or when clinically indicated. Additional radiographic evaluation, such as bone scan and/or CT, was performed at the discretion of the treating physician. Detection of cancer in the ureter and/or urethra was coded as a second (metachronous) primary and not as local or distant recurrence. When patients died, the cause of death was determined by the treating physicians by chart review corroborated by death certificates or by death certificates alone. Patients who were identified as having died of bladder cancer had progressive, widely disseminated, and often highly symptomatic metastases at the time of death. Perioperative mortality (death within 30 d of surgery) was censored at time of death for bladder cancer–specific survival analyses.

2.4. Statistical analysis

Differences in categorical and continuous variables between pT2a and pT2b substages were tested using the chi-square and Mann-Whitney *U* test, respectively. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RC. In all models, proportional hazards assumptions were

Table 1 – Clinical and pathologic characteristics of 565 patients with pT2 urothelial carcinoma of the bladder at radical cystectomy

	Total	pT2a	pT2b	*p* value (pT2a vs pT2b)	pT2a LN negative	pT2b LN negative	*p* value (pT2a LN negative [%] vs pT2b LN negative [%])
Overall, No.	565	249	316	–	207	233	–
Age, yr, median; IQR	66.2; 12.9	66.0; 12.4	66.9; 13.7	0.259	66.3; 12.5	67.0; 13.9	0.921
LNs removed, median; IQR	21; 26.8	22; 29.0	19; 23.5	0.104	22; 27.0	19; 22.0	0.089
Gender, *n* (%)							
Males	434 (76.8)	205 (82.7)	229 (73.2)	0.008	171 (82.6)	170 (73.0)	0.016
Females	127 (22.5)	43 (17.3)	84 (26.8)		36 (17.4)	63 (27.0)	
Grade, *n* (%)				0.012			0.041
1	8 (1.4)	5 (2.0)	3 (0.9)		5 (2.4)	3 (1.3)	
2	410 (72.6)	194 (77.9)	216 (68.4)		163 (78.7)	163 (70.0)	
3	147 (26.0)	50 (20.1)	97 (30.7)		39 (18.8)	67 (28.8)	
LN status, *n* (%)							
pN0	440 (77.9)	207 (84.5)	233 (76.1)	0.015	207 (100.0)	233 (100.0)	–
pN1–2	111 (19.6)	38 (15.5)	73 (23.9)		0 (0)	0 (0)	
STSM status, *n* (%)							
Negative	546 (96.6)	243 (97.6)	303 (96.5)	0.451	202 (97.6)	225 (97.4)	0.903
Positive	17 (3.0)	6 (2.4)	11 (3.5)		5 (2.4)	6 (2.6)	
LVI, *n* (%)							
Negative	338 (59.8)	153 (67.4)	185 (64.0)	0.422	138 (73.8)	148 (70.1)	0.418
Positive	178 (31.5)	74 (32.6)	104 (36.0)		49 (26.2)	63 (29.9)	
Concomitant CIS, *n* (%)							
Negative	295 (52.2)	116 (46.6)	179 (57.2)	0.012	96 (46.4)	130 (56.5)	0.034
Positive	267 (47.3)	133 (53.4)	134 (42.8)		111 (53.6)	100 (43.5)	
Adjuvant chemotherapy, *n* (%)							
Negative	464 (82.1)	218 (87.6)	246 (77.8)	0.003	202 (97.6)	205 (88.0)	0.000
Positive	101 (17.9)	31 (12.4)	70 (22.2)		5 (2.4)	28 (12.0)	

CIS = carcinoma in situ; IQR = interquartile range; LN = lymph node; LVI = lymphovascular invasion; STSM = soft-tissue surgical margin.

systematically verified using the Grambsch-Therneau residual-based test. All reported *p* values are two sided, and statistical significance was set at $p < 0.05$. No adjustments were made for multiple statistical tests. All statistical tests were performed with SPSS, v.17.0.0 (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Clinical and pathologic characteristics

Five hundred and sixty-five patients (21.7%) had pT2 UCB at RC. Median age in the entire pT2 group was 66.2 yr (interquartile range [IQR]: 12.87). Of the 565 patients, 249 patients (44.1%) had superficial (pT2a) and 316 patients (55.9%) had deep (pT2b) muscle invasion. Table 1 compares the clinical and pathologic features of these patients. One hundred and eleven patients (19.6%) had metastases to regional lymph nodes, leaving 207 patients with pT2a node-negative disease and 233 patients with pT2b node-negative disease. There was no difference in age, proportion of LVI, surgical margin status, and number of lymph nodes removed between pT2 substages (Table 1). In both the entire group as well as the node-negative patients, the pT2b patients had a significantly higher proportion of women ($p = 0.008$ and $p = 0.016$, respectively), pathologic tumor grade ($p = 0.012$ and $p = 0.041$, respectively), proportion of lymph node metastasis ($p = 0.015$), and lower rate of concomitant CIS ($p = 0.012$ and $p = 0.034$, respectively) compared with pT2a patients.

3.2. Clinical outcomes

Median follow-up was 50.5 mo (IQR: 88.4) for patients alive at last follow-up. Disease recurrence occurred in 169 patients (29.9%). A total of 265 (46.9%) were deceased at the time of analysis including 139 patients (24.6%) who died of UCB.

Overall, 5-yr recurrence-free and cancer-specific survival estimates in the pT2a patients were 73.2% (95% confidence interval [CI], 67–79) and 78.0% (95% CI, 72–83), respectively, compared to 58.7% (95% CI, 52–65) and 65.1% (95% CI, 59–71) for pT2b patients ($p = 0.002$ and $p = 0.001$, respectively) (Fig. 1A and B). These differences in survival remained significant when restricting analyses to lymph node–negative patients (Fig. 1C and D).

In univariable analyses, age at time of radical cystectomy, gender, surgical margin status, and grade (all *p* values > 0.05) were not associated with disease recurrence or cancer-specific survival (not shown).

In multivariable analyses, LVI ($p = 0.014$ and $p = 0.018$, respectively), lymph node involvement ($p = 0.002$ and $p = 0.027$, respectively), and pT2b substage ($p = 0.011$ and $p = 0.006$, respectively) were independently associated with disease recurrence and cancer-specific mortality (Table 2). When analyses were restricted to pT2 lymph node–negative patients, LVI ($p = 0.002$ and $p = 0.002$, respectively) and

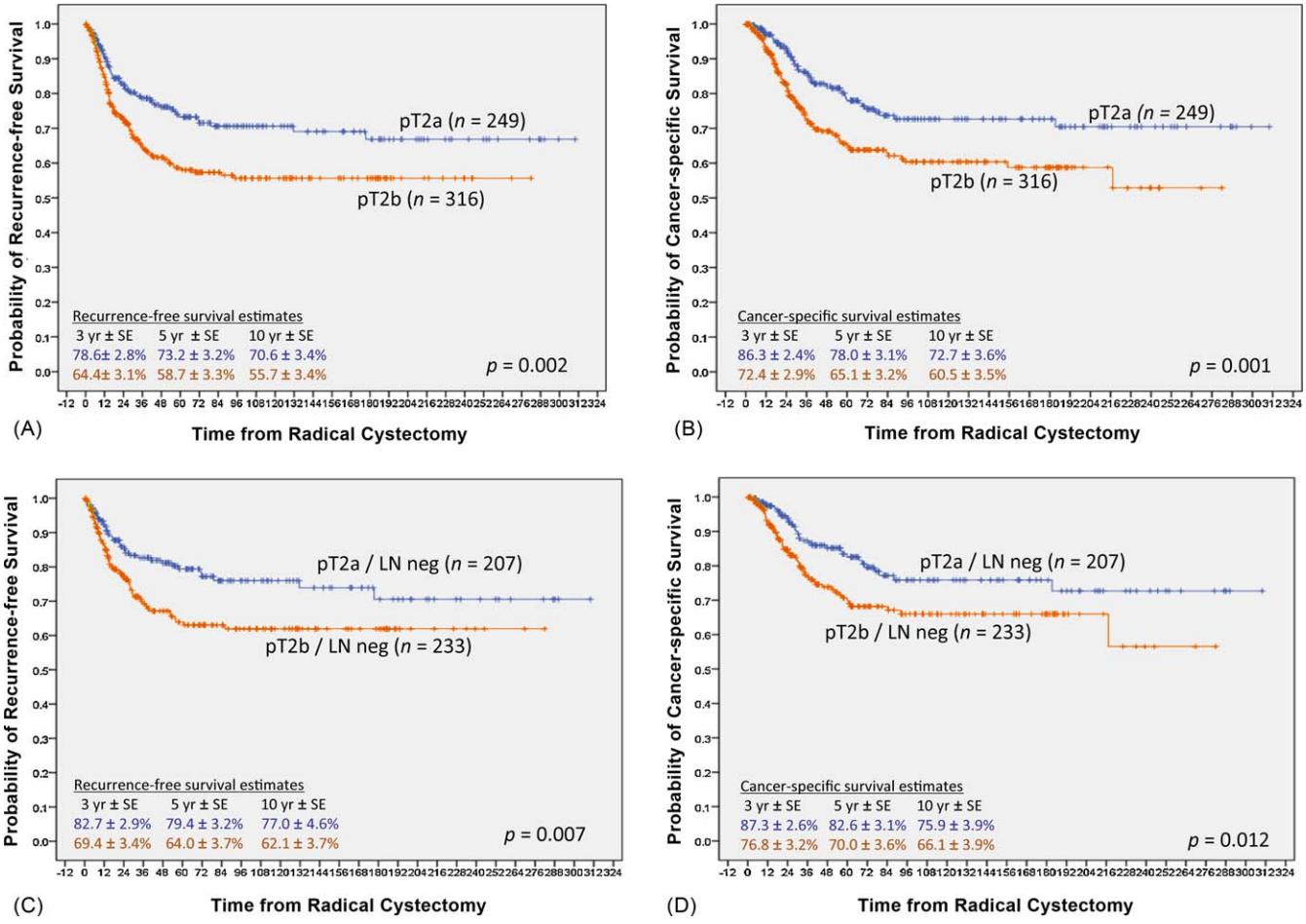

Fig. 1 – Probability estimates of (A) recurrence-free and (B) cancer-specific survival in 565 patients with pT2 urothelial carcinoma of the bladder (UCB) at radical cystectomy (RC) stratified by pT2 substage. Probability estimates of (C) recurrence-free and (D) cancer-specific survival in 440 patients with pT2 lymph node (LN)–negative UCB at RC stratified by pT2 substage.
SE = standard error.

pT2b substage ($p = 0.003$ and $p = 0.005$, respectively) remained significantly associated with both disease recurrence and cancer-specific mortality (Table 3).

4. Discussion

Despite the large body of literature on outcomes after RC in patients with UBC and the strong prognostic value of pathologic tumor stage, there are contradictory data on the significance of the extent of muscle invasion (superficial vs deep) on clinical outcome [3–8]. In 1952, Jewett proposed the subdivision of pT2 disease according to depth of muscle invasion with pT2a involving the inner half and pT2b involving the outer half of the muscular wall based on survival differences observed in only 18 patients [16]. In 1997, the AJCC included the substaging of pT2 tumors in the TNM criteria [9]. However, multiple studies have reported no prognostic value of pT2 substaging (Table 4) [10–15].

Table 2 – Multivariate Cox regression analyses predicting disease recurrence and cancer-specific survival in 565 patients with pT2 urothelial carcinoma of the bladder at radical cystectomy

Variable	Disease recurrence			Cancer-specific death		
	HR	95% CI	p	HR	95% CI	p
Age	0.999	0.984–1.015	0.911	1.004	0.988–1.022	0.606
Gender	1.161	0.808–1.669	0.418	1.267	0.855–1.877	0.238
Grade	0.943	0.689–1.414	0.943	0.883	0.589–1.325	0.548
Lymph node metastasis	1.758	1.227–2.518	0.002	1.574	1.054–2.350	0.027
Lymphovascular invasion	1.538	1.092–2.166	0.014	1.582	1.082–2.314	0.018
Soft-tissue surgical margin status	1.477	0.649–3.361	0.353	1.227	0.450–3.345	0.689
Substage pT2b	1.550	1.107–2.169	0.011	1.696	1.167–2.466	0.006

CI = confidence interval; HR = hazard ratio.

Table 3 – Multivariate Cox regression analyses predicting disease recurrence and cancer-specific survival in 440 patients with pT2 node-negative urothelial carcinoma of the bladder at radical cystectomy

Variable	Disease recurrence			Cancer-specific death		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.001	0.982–1.020	0.914	1.007	0.987–1.029	0.487
Gender	1.023	0.645–1.622	0.925	1.105	0.672–1.818	0.694
Grade	0.930	0.596–1.450	0.748	1.004	0.619–1.627	0.988
Lymphovascular invasion	1.898	1.262–2.853	0.002	2.033	1.298–3.186	0.002
Soft-tissue surgical margin status	1.416	0.516–3.886	0.499	0.904	0.220–3.703	0.888
Substage pT2b	1.858	1.227–2.814	0.003	1.909	1.210–3.009	0.005

CI = confidence interval; HR = hazard ratio.

Table 4 – Five-year recurrence-free survival of patients with pT2a and pT2b urothelial carcinoma of the bladder at radical cystectomy

References	Patients, No.				5-yr recurrence-free survival, %					
	pT2a	pT2b	pT2a LN negative	pT2b LN negative	pT2a	pT2b	*p* value	pT2a LN negative	pT2b LN negative	*p* value
Boudreaux et al [10]	–	–	59	64	–	–	–	52.8	49.6	0.89
Cheng et al [11]*	31	33	26	28	82	79	0.20	84	87	0.75
Girgin et al [12]	–	–	35	40	–	–	–	84	66	NS
Herranz Amo et al [13]#	25	17	–	–	66	60	0.52	–	–	–
Tokgoz et al [14]	35	22	–	–	69.1	66.1	0.896	–	–	–
Yu et al [15]	147	164	127	115	80	67	0.021	86	75	0.091
Ghoneim et al [17]+	1330	407	373	1077	75.1	53.2	0.001	76.6	58.4	0.01
Present series	249	316	207	233	73.2	58.7	0.002	79.4	64.0	0.007

LN = lymph node; NS = not significant.
* Percentage of distant metastasis-free survival at 10 yr.
# Five-year cancer-specific survival.
+ Included 30% of transitional cell carcinoma.

These studies were limited by their small sample sizes and single-institution nature. Therefore, we assessed the prognostic value of pT2 substaging in a large multicenter study.

We found that patients with pT2b UCB had a significantly worse outcome compared with patients with pT2a disease regardless of other classic pathologic features such as lymph node status and the presence of LVI. Yu et al found a difference in outcomes when comparing pT2a versus pT2b patients; however, this difference was not statistically significant after adjusting for the effect of lymph node metastasis [15]. The authors hypothesized that the depth of muscle invasion is related to the incidence of lymph node involvement and that pT2 substaging does not add prognostic information when lymph node status is known. However, they used adjuvant chemotherapy in a significant proportion of the pT2b patients as compared with pT2a patients (33% vs 12%, respectively) that may have obscured the association of deep muscle invasion with outcomes. In a study of 64 patients with pT2 UCB, Cheng et al found that tumor size was associated with distant metastasis-free and cancer-specific survival, whereas substaging of pT2 was not [11]. In contrast, Ghoneim et al reported a significant difference in 5-yr recurrence-free survival between pT2a and pT2b tumors (75.1% vs 53.2%, respectively) that was maintained after stratification by lymph node metastasis [17]. Their study, however, consisted of 54% of patients with squamous cell carcinomas.

Similarly to previous studies, we found that patients with deep muscle invasion (pT2b) were significantly more likely to harbor lymph node metastasis than those with superficial muscle invasion (pT2a) [15,17]. However, in our series, pT2 substaging had an independent prognostic role once adjusted for the presence of lymph node metastases. Interestingly, the presence of LVI also reconfirmed its major prognostic value for prediction of both recurrence and survival in patients with pT2 UCB [18,19].

In the current study, adjuvant chemotherapy did not improve cancer-related outcomes of pT2 UCB patients. However, we were not able to control for the regimen, number of cycles, and response criteria. Thus we cannot draw conclusions regarding the impact of optimized adjuvant chemotherapy in these patients. The role of adjuvant therapy can only be assessed in large prospective trials.

Our study had several important limitations. First and foremost are the limitations inherent to retrospective analyses. Another limitation is that we did not review all pathologic specimens. Moreover, we excluded all patients treated with preoperative chemotherapy, potentially creating a bias. Furthermore, the population in this study underwent surgery by multiple surgeons and had specimens evaluated by multiple pathologists. However, this can be construed as a strength because it stands for a real-world practice, making the conclusions of the study more generalizable. The analysis of patients treated in referral centers may have biased the results. Finally, the study period spans >25 yr, and the data in the present study may not represent current practice patterns, considering that diagnostic tools, surgical techniques, perioperative care, the

number of lymph nodes removed, indication for surgery, administration of perioperative chemotherapy, regimen of chemotherapy, and follow-up protocols might have changed over time. However, 28% of the patients in the study were treated in the 1990s, and 48% in the year 2000 or thereafter, which may limit the relevance of such issues.

5. Conclusions

In this large international cohort, we found that pT2 substaging based on depth of muscle invasion can stratify patients into statistically significantly different risk groups with regard to outcomes. This strong association was independent of lymph node status and other clinicopathologic features. Therefore, we believe that pT2 substaging should be maintained in the AJCC TNM staging because it may add prognostic value and may help in the application of future therapeutic approaches.

Author contributions: Shahrokh F. Shariat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tilki, Reich, Shariat.
Acquisition of data: Tilki, Reich, Karakiewicz, Novara, Kassouf, Ergün, Fradet, Ficarra, Sonpavde, Stief, Skinner, Svatek, Lotan, Sagalowsky, Shariat.
Analysis and interpretation of data: Tilki, Reich, Shariat.
Drafting of the manuscript: Tilki, Reich, Shariat.
Critical revision of the manuscript for important intellectual content: Karakiewicz, Novara, Kassouf, Ergün, Fradet, Ficarra, Sonpavde, Stief, Skinner, Svatek, Lotan, Sagalowsky.
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