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Rates of lymph node invasion and their impact on cancer specific mortality in upper urinary tract urothelial carcinoma

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ABSTRACT

Purpose: To analyze lymph node invasion (LNI) rates according to tumor characteristics and to test the impact of LNI and its extent on cancer specific mortality (CSM) in surgically-treated non metastatic urothelial upper urinary tract carcinoma (UTUC) patients.
Materials and methods: Within the SEER database (2004–2014), we identified 2098 patients with histologically confirmed non-metastatic urothelial carcinoma of renal pelvis or ureter who underwent NU with LND. LNI rates stratified according to tumor location and stage were described. Kaplan-Meier plots illustrated CSM rates according to LNI and its extent. Multivariable Cox regression models (MCRMs) tested the effect of LNI and its extent on CSM.
Results: Of 2098 UTUC patients, who underwent nephroureterectomy with lymph node dissection, 646 (33%) had LNI. The median number of removed lymph nodes was 3 [Interquartile range (IQR): 1–7]. The median number of positive lymph nodes in patients, who harbored LNI was 1 (IQR:1–3). LNI rates according to tumor location were, respectively, 23.6% for ureteral and 36.5% for renal pelvis tumors. LNI rates according to tumor stage were 9.6, 18.0, 38.7 and 63.9%, for respectively, T1, T2, T3 and T4 UTUC. In MCRMs, LNI achieved independent predictor status for higher CSM (HR 3.00; $p < 0.001$). Finally, in MCRMs, number of positive lymph nodes defined as the 75th percentile ($n \geq 3$) achieved independent predictor status for higher CSM (HR 1.37; $p = 0.04$).
Conclusions: LNI in non-metastatic UTUC patients is the most important determinant of CSM. Number of positive lymph node is independently associated with higher CSM. In consequence, lymph node dissection can provide extensive prognostic information.

Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a rare entity [1,2] and large scale series examining the history of surgically-treated non-metastatic UTUC are scarce. The standard of care for management of high risk (presence of hydronephrosis, size > 2 cm, high-grade cytology or biopsy, multifocal pattern or previous cystectomy for bladder cancer) UTUC is nephroureterectomy (NU) with or without lymph node dissection (LND) [3]. According to European Urological Association (EAU) guidelines [3] and National Comprehensive Cancer Network (NCCN) guidelines [4], LND should only be performed in select patients that harbor high grade UTUC (recommended by the NCCN Guidelines) and/or T-stage higher than T1 (EAU Guidelines). Although the therapeutic role of LND at

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NU is debatable [5–10], LND has a central role for providing optimal staging information. The need for most detailed staging has become even more important with the advent of novel systemic therapies, capable of providing greater survival benefit than historic chemotherapy. Unfortunately, few investigations focused on contemporary UTUC patients with the intent of examining the value of staging information that can be derived from either the primary tumor or locoregional lymph nodes. Based on this unmet need, we decided to perform a systematic assessment of primary UTUC and locoregional lymph nodes characteristics with respect of their predictive and prognostic value. We hypothesized that primary tumor characteristics (tumor stage and tumor location) represent accurate predictors of LNI and that lymph node characteristics represent a predictor of cancer specific mortality (CSM). To test our hypothesis we relied on the Surveillance, Epidemiology and End Results (SEER) database.

Patients and methods

Study population

Within the SEER database (2004–2014), we identified 2098 patients with histologically confirmed non-metastatic urothelial carcinoma of renal pelvis or ureter who underwent NU with LND. Patients with unknown tumor stage and patients aged <18 years were excluded.

Definition of variables for analyses

Patients were stratified according to presence or absence of LNI. Covariates consisted of number of removed lymph nodes, number of positive lymph nodes, tumor stage (T1/T2, T3/T4), tumor grade (low grade, high grade), tumor location (renal pelvis, ureter), chemotherapy administration (Yes, No/Unknown), laterality (left, right), gender (male, female), age at diagnosis (65<,65–72,73-79,≥80), race (Caucasian, African-American, other), year of diagnosis (2004–2008 and 2009–2014) and marital status (married, unmarried). CSM was defined according to SEER mortality code. All other deaths were considered as other-cause mortality.

Statistical analysis

Descriptive statistics focused on frequencies and proportions for categorical variables. The statistical significance of differences in medians and proportions was tested with the Kruskal-Wallis and chi-square tests. All statistical tests were two-sided with a significance level set at $p < 0.05$. First, we tested the annual LNI rates. Estimated annual percentage changes (EAPC) were tested with the least squares linear regression [11]. Second, adjusted LNI rates according to tumor location and tumor stage were generated by multivariable logistic regression models [12]. Third, Kaplan-Meier plots illustrated CSM rates according to LNI. Fourth, multivariable Cox regression models (MCRMs) tested the effect of LNI on CSM. Fifth, Kaplan-Meier plots illustrated CSM rates according to number of positive lymph nodes. Sixth, MCRMs tested the effect of number of positive lymph nodes on CSM. Specifically, we relied on three different metrics to code the number of positive lymph nodes in UTUC patients, with respect of a potential effect on CSM. Here, we relied on continuously coded lymph node counts and on stratification according to median and on the 75th percentile of the number of positive lymph nodes. Analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1) [13].

Table 1
Baseline characteristics of 2098 upper urinary tract urothelial carcinoma patients who underwent nephroureterectomy with lymph node dissection (Surveillance, Epidemiology, and End Results registry 2004–2014).

		Overall (N = 2098) (%)	Without Lymph Node Invasion (N = 1411) (67%)	With Lymph Node Invasion (N = 687) (33%)	p-Value
Number of remove lymph nodes	Mean	6	5	6	<0.001
	Median	3 (1–7)	3 (1–7)	3 (1–8)	<0.001
Number of positive lymph nodes	Mean	/	/	2.7	
	Median	/	/	1 (1–3)	
Lymph node density	Mean	/	/	0.7	
	Median	/	/	0.8 (0.3–1)	
T-Stage	T1	470 (22.4)	426 (30.2)	44 (6.4)	<0.001
	T2	342 (16.3)	281 (19.9)	61 (8.9)	
	T3	991 (47.2)	599 (42.5)	392 (57.1)	
	T4	295 (14.1)	105 (7.4)	190 (27.7)	
Grade	High Grade	1714 (81.7)	1085 (76.9)	629 (91.6)	<0.001
	Low Grade	247 (11.8)	223 (15.8)	24 (3.5)	
	Unknown	137 (6.5)	103 (7.3)	34 (4.9)	
Location	Pelvis	1441 (68.7)	908 (64.4)	533 (77.6)	<0.001
	Ureter	657 (31.3)	503 (35.6)	154 (22.4)	
Laterality	Left	1172 (55.9)	779 (55.2)	393 (57.2)	0.4
	Right	926 (44.1)	632 (44.8)	294 (42.8)	
Chemotherapy	No/Unknown	1490 (71)	1148 (81.4)	342 (49.8)	<0.001
	Yes	608 (29)	263 (18.6)	345 (50.2)	
Age (years)	<65	575 (27.4)	392 (27.8)	183 (26.6)	0.5
	65–72	548 (26.1)	376 (26.6)	172 (25)	
	73–79	508 (24.2)	328 (23.2)	180 (26.2)	
	>80	467 (22.3)	315 (22.3)	152 (22.1)	
Gender	Female	873 (41.6)	568 (40.3)	305 (44.4)	0.1
	Male	1225 (58.4)	843 (59.7)	382 (55.6)	
Race	Caucasian	1809 (86.2)	1207 (85.5)	602 (87.6)	0.4
	African American	110 (5.2)	79 (5.6)	31 (4.5)	
	Others	179 (8.5)	125 (8.9)	54 (7.9)	
Year of Diagnosis	2004–2008	1085 (51.7)	722 (51.2)	363 (52.8)	0.5
	2009–2014	1013 (48.3)	689 (48.8)	324 (47.2)	

Table 2
Multivariable Cox regression model predicting cancer specific mortality in 2098 upper urinary tract urothelial carcinoma patients who underwent nephroureterectomy with lymph node dissection (Adjusted for number of removed nodes, tumor location, laterality, chemotherapy administration, race and year of diagnosis).

		HR (95% CI)	p-Value
Lymph node invasion	No	(Ref)	
	Yes	2.78 (2.27–3.40)	<0.001
T-stage	T1	(Ref)	
	T2	1.91 (1.25–2.91)	0.03
	T3	3.02 (2.01–4.34)	<0.001
	T4	5.41 (3.65–8.02)	<0.001
Grade	High Grade	(Ref)	
	Low Grade	0.60 (0.40–0.92)	0.02
	Unknown	1.24 (0.82–1.87)	0.3
Age (years)	1.02	1.01–1.03	<0.001
Gender	Female	(Ref)	
	Male	0.77 (0.64–0.92)	0.01

Abbreviations: Hazard Ratio (HR), Confidence interval (CI).

Results

General characteristics of the study populations

Of 2098 UTUC patients the majority were male (58.4%) and Caucasian (86.2%). Median age was 72 years (Interquartile range 65–80 years). Overall, 470 patients harbored T1 (22.4%) vs 342 T2 (16.3%) vs 991 T3 (47.2%) vs 295 T4 (14.1%) stage. Over 80% of patients harbored high grade. The tumor location was divided between ureteral (31.3%) and pelvic (68.7%).

Overall, 646 harbored LNI (33%). LNI patients had higher number of removed lymph nodes (mean 6 vs 5; $p < 0.001$), as well as higher stage (T3/T4: 84.7 vs 49.9%; $p < 0.001$) (Table 1) and more frequently harbored high grade tumors (91.6 vs 76.9%; $p < 0.001$). Rates of LNI did not change over time (EAPC -0.2%; $p = 0.8$). Lymph node invasion rates according to tumor location were, respectively, 23.4% for ureteral and 36.5% for renal pelvis tumors (Supplementary Fig. 1). However, no difference in number of removed nodes was recorded according to tumor location. Finally, LNI rates according to tumor stage were, 9.6, 18.0, 38.7 and 63.9% for, respectively, T1, T2, T3 and T4 UTUC (Fig. 1).

Survival analyses according to lymph node invasion

Median follow-up was 28 months. 5-year CSM rate for the entire cohort was 34%. After stratification according to T-stage, 5-year CSM rates were 10% in T1 N0 and 33% in T1 N1-3 vs 19% in T2 N0 and 51% in T2 N1-3 vs 31% in T3 N0 and 62% in T3 N1-3 vs 39% in T4 N0 and 77% in T4 N1-3 (all $p < 0.001$) (Fig. 2a–d). In MCRMs, T-stage achieved independent predictor status for higher CSM: T2 (HR 1.91, CI 1.25–2.91; $p = 0.03$), T3 (HR 3.02, CI 2.01–4.34; $p < 0.001$), T4 (HR 5.41, CI 3.65–8.02; $p < 0.001$). Similarly, LNI also achieved independent predictor status for higher CSM (HR 2.78, CI 2.27–3.40; $p < 0.001$). Conversely, tumor location failed to achieve independent predictor status for higher CSM (HR 0.96, CI 0.78–1.18; $p = 0.9$) (Table 2). Finally the interaction term examining the combined effect of tumor stage and LNI failed to achieve independent predictor status.

Survival analyses according to number of positive lymph nodes

In univariable and MCRMs predicting CSM according to continuously coded number of positive lymph nodes, the latter achieved independent predictor status for higher CSM (HR 1.04, CI 1.01–1.08; $p = 0.02$).When analyses were stratified according to median number of positive lymph nodes (1 and > 1), in LNI patients, no CSM difference was found in either univariable analyses (5-year median CSM rates 60 vs 65%; p-value = 0.2) (Fig. 3a) or in MCRMs (HR 1.22, CI 0.94–1.59; $p = 0.1$). Finally, when analyses were performed according to the 75th percentile number of positive lymph nodes (<3 and ≥ 3), CSM difference was found both in univariable analyses (5-year median CSM rates 60 vs 71%; p-value = 0.04) (Fig. 3b). and MCRMs (HR 1.37, CI 1.02–1.85; $p = 0.04$).

Discussion

UTUC is a rare entity. Few data are available regarding the natural history of surgically-treated UTUC and the predictive and

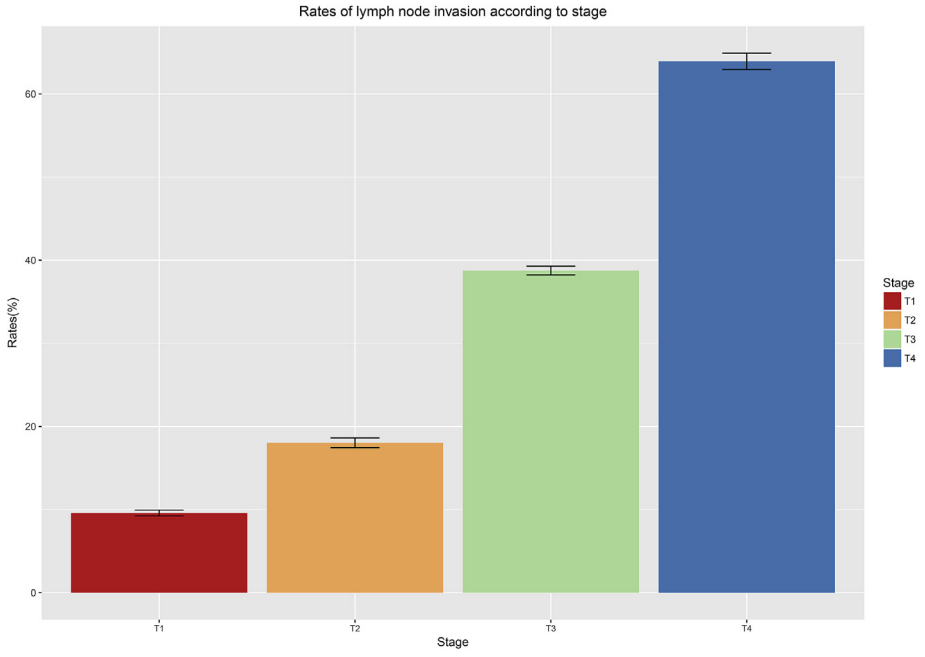

Fig. 1. Rates of lymph node invasion according to stage.

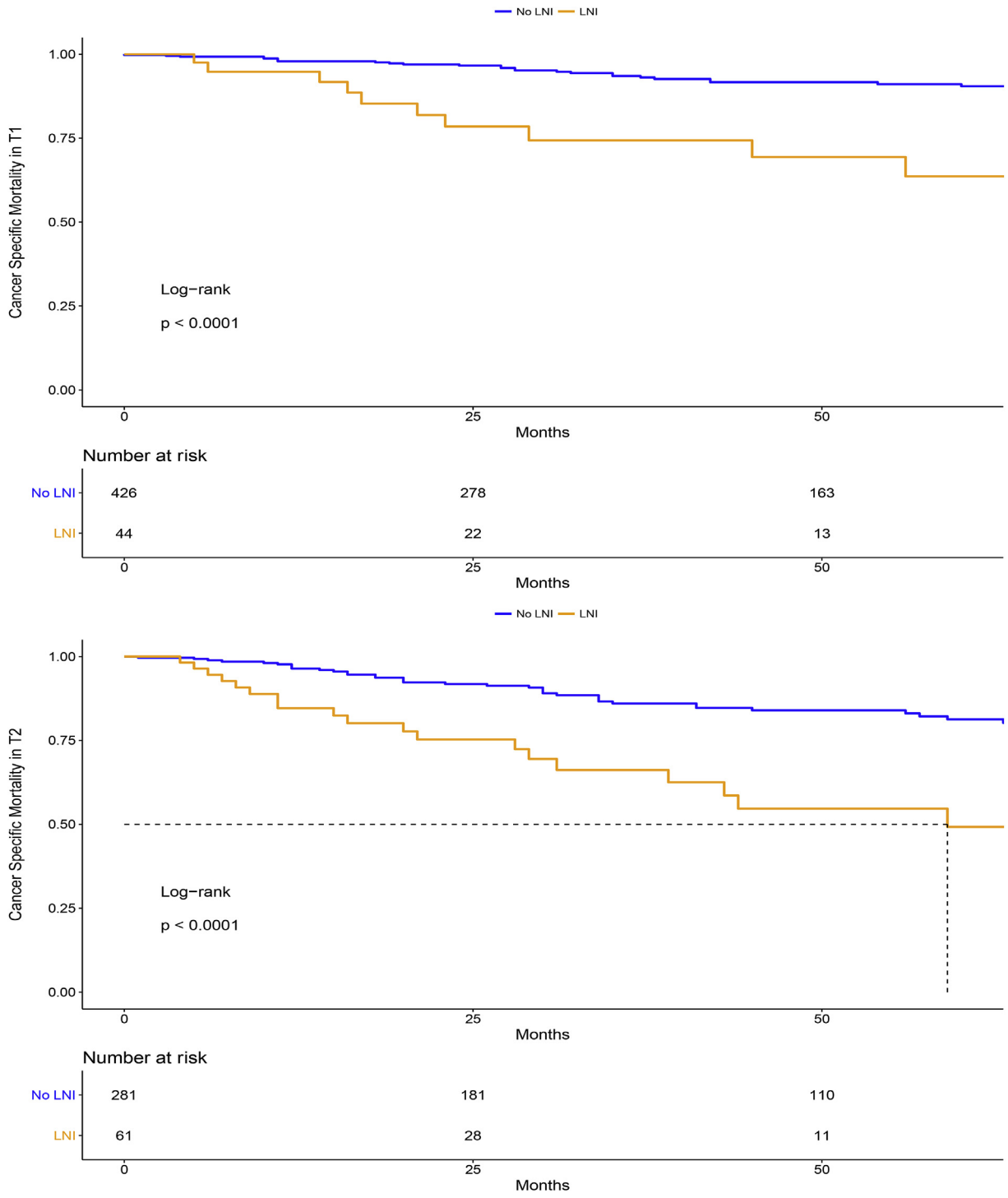

Fig. 2. a-d. Kaplan-Meier plots depicting the effect of lymph node invasion on cancer specific mortality according to tumor stage in 2098 non metastatic upper urinary tract urothelial carcinoma patients.

prognostic value of primary tumor and/or lymph node characteristics. Based on this consideration, we tested the predictive and prognostic ability of primary tumor and lymph node characteristics within a large, contemporary, population-based cohort. We hypothesized that primary tumor characteristics can predict LNI. Moreover, we postulated that the combined input originating from tumor stage, its location, as well as LNI and its extent can predict CSM. Our study revealed several important findings.

First, UTUC was similarly distributed within men and women (58.4% and 41.6%). This findings distinguishes UTUC from urothelial bladder cancer [14,15], where the vast majority of patients are men. These most contemporary gender specific figures contrast with more historical estimates, where UTUC prevalence was higher in males [1,16]. Higher rates of tobacco exposure in females and other

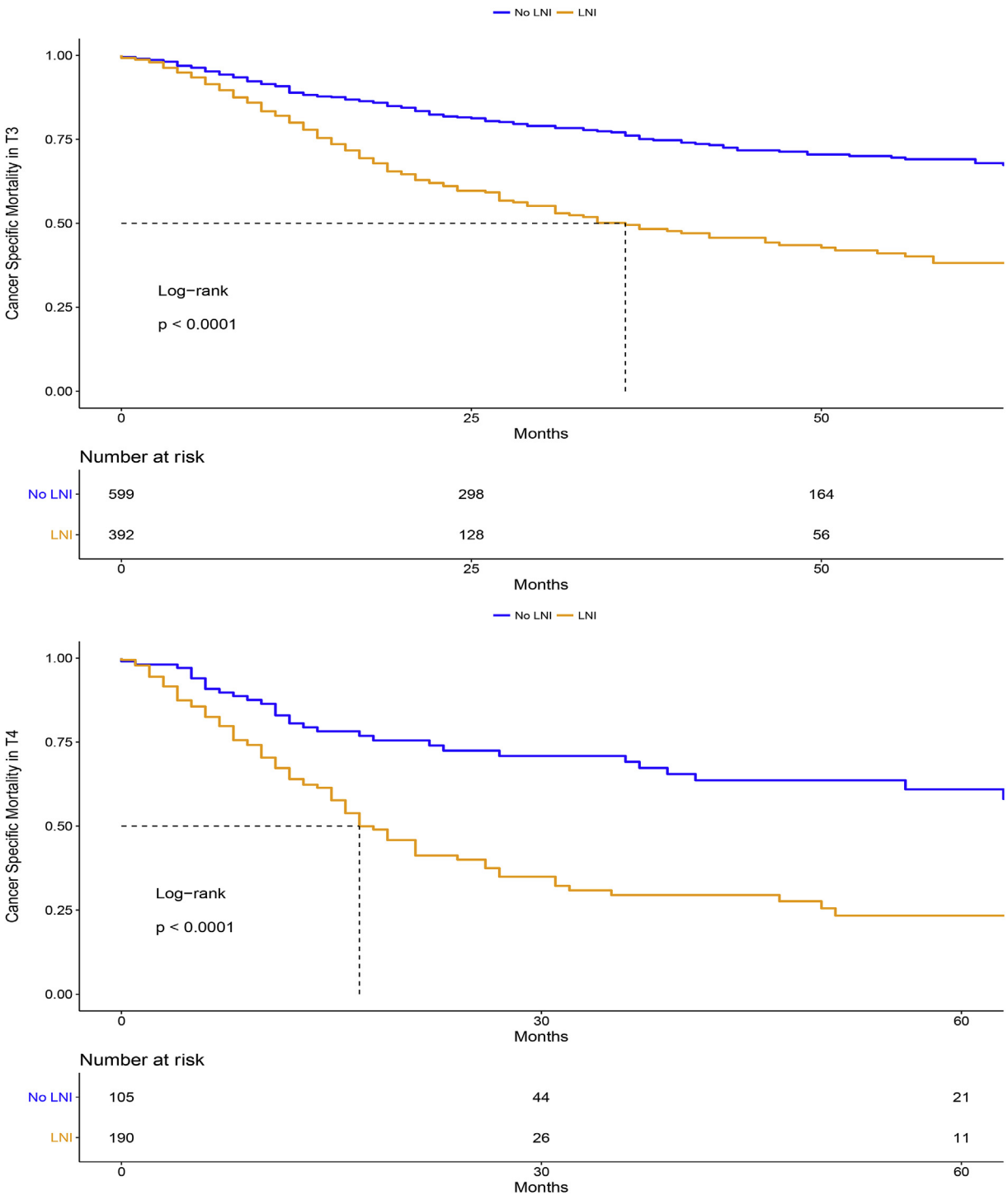

Fig. 2. (*continued*).

genetic and/or environmental changes may be responsible for this difference [17,18]. Additionally, a selection bias within the current database may also have contributed to a chance phenomenon.

Regarding primary tumor characteristics several findings are noteworthy. First and foremost, 81.7% patients harbored high grade tumors. This finding is an agreement with the NCCN guidelines recommendation for NU in this patient population [4]. Organ confined UTUC, defined as T1 or T2 stage, was recorded in 38.7% of patients. Conversely, 61.3% harbored non organ confined UTUC. Similarly, 33% of the patients harbored LNI. Both observations are worrisome and indicate that the decision to perform a NU is overwhelmingly frequently made, when UTUC is no longer organ confined. Unfortunately, our database does not allow us to discriminate between de novo, non-organ-confined T3/T4 and/or N1–N3 patients, relative to those who progressed from organ confined stages. Nonetheless, the urologic community deserves to be sensitized about the importance of earlier NU to provide a better chance for cure at an organ confined disease stage. The reported

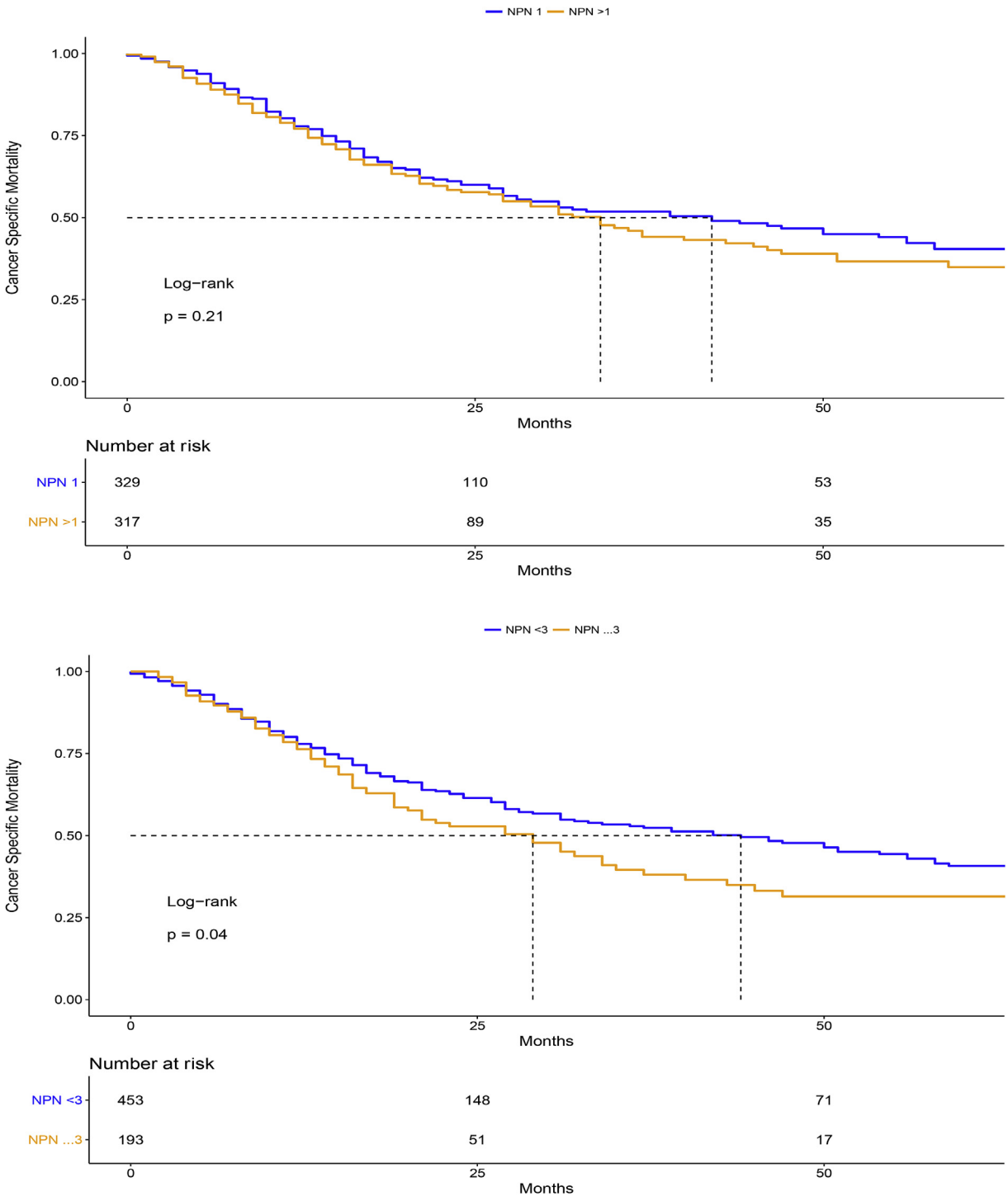

Fig. 3. a-b. Kaplan-Meier plots depicting the effect of number of positive lymph nodes on cancer specific mortality according to the median (n = 1) and the 75th percentile (n = 3) in 646 non metastatic upper urinary tract urothelial carcinoma patients with lymph node invasion and available lymph node counts.

rates do need to be taken in account with respect to the nature of the population that includes only those individuals, who underwent LND. However, the rate of T3/4 UTUC in those without LNI accounted for 50% of cases.

Regarding tumor location, most patients with LNI harbored pelvic tumors. This finding is consistent with previous analyses. Tumor location according pelvis vs ureter definition was associated with higher rates of LNI, even after adjustment for all other covariates. However, tumor location was not an independent predictor of CSM (HR 0.96, CI 0.78–1.18; p = 0.9). This observation indicates a differential rate of LNI. The latter, might be related to differences in location-specific tumor phenotype. Alternatively, it may also be related with LND template [7], which may differ between patients with renal pelvis vs ureteral tumors.

When tumor stage was tested with respect to its ability to predict LNI, it emerged as independent predictor. Specifically, patients with T3/T4 tumors had 2.5 higher probability of LNI compared to their T1/T2 counterparts. From a clinical prospective,

these observations validate the recommendation for LND in patients with stage T2 or higher UTUC, since those patients' LNI rates range from 20 to 64% vs 10% in T1 patients. Existing guidelines do not base their LND recommendations according to tumor location. However, in our analyses tumor location resulted in differences that might warrant consideration. But as previously discussed, such differences may have originated from the confounding effect of LND template according to tumor location. In consequence a meaningful recommendation for or against LND cannot be made according tumor location (pelvic or ureteral).

Regarding the effect of LNI and its effect on CSM, additional important observations deserve mention. First, patient with LNI had 3-fold higher rate of CSM. This observation validates previous reports [19–22], where LNI represented a significant and highly clinically meaningful predictor of cancer control, regardless of the addressed endpoint. Additionally, and unlike in previous analyses, we tested the prognostic ability of LNI extent in CSM analyses. These results demonstrated that LNI extent, coded according to positive lymph node counts in continuous fashion or according to positive lymph node cut-off defined as the 75th percentile ($n = 3$), achieved independent predictor status for higher CSM rates. This observation implies that a critical number of positive lymph nodes discriminates between patients with highly unfavourable vs more favourable prognosis. The range of removed lymph nodes was 1–38 (median 3, IQR 1–7). This observation indicates that the vast majority of patients (75%) have only had up to 7 lymph nodes removed and 50% only had 3 lymph nodes removed. In consequence, the extent of LND at NU is limited. This limitation is particularly noticeable, when LND at NU is compared to LND at radical prostatectomy [23] or radical cystectomy [24,25]. However, when LND at NU is compared to LND at nephrectomy, similar nodal yield is seen [26]. This implies that most lymph nodes are resected from peri-hilar tissue at UTUC and that the added yield of LNI from lymph nodes situated within periureteral tissue is very limited.

Regarding LNI and positive lymph nodes, our data showed that the vast majority of patients with LNI (75%) harboured 2 or less positive lymph nodes and 50% only harbored 1 positive lymph node. This low positive lymph node count corroborate the relatively limited extent of LND at NU. Our findings are in agreement with a recent report focusing on LND extent and its effect on CSM. In this report Chappidi et al. [5] demonstrated lower CSM rates in patients with 5 or more removed lymph nodes. In our report, we showed statistically significantly higher CSM according to the number of positive lymph nodes. This direct relationship was strongest, when the positive lymph node counts exceeded 3, which corresponds to the 75th percentile of positive lymph nodes counts. Our cut-off analyses based on the median, which represents 1 positive lymph node, failed to result in statistically significant findings in multivariable analyses. The discordance of our findings according to different cut-off values (median vs 75th percentile) is most-likely related to the narrow distribution of positive lymph nodes counts that lack granularity. Nonetheless, our findings, convincingly indicate that the burden of positive lymph nodes is an indicator of disease aggressiveness, when CSM is used as an end point.

In summary, we observed an elevated rate of non-organ-confined UTUC at NU, even in patients without LNI (50%). Moreover, we observed an increase of LNI rates between T1 (9.6%) and T2 (18%) patients with an exponential increase in LNI in T3 (38.7%) and T4 (63.9%) stages. Finally, we observed appreciably higher CSM in presence of LNI and a dose response effect that directly depends on the number of positive lymph nodes, either in continuously coded or categorical analyses. These observations provide a significant contribution to the knowledge of the natural history of UTUC in patients treated with NU and LND.

Our study is not devoid of limitations. First, heterogeneity regarding tumor stage and grade evaluation may be present because central pathology review was not performed. Second, the site of removed lymph nodes was not assessed and no standardized template was used. Third, no information was available about lymphovascular invasion. The latter is considered as an important predictor of LNI and/or CSM. Fourth, timing and chemotherapy composition were not considered in this data repository. Fifth, detailed information regarding surgical technique and distal ureter management during laparoscopic and robotic surgery were not available. Sixth, according to SEER database no distinction between different ureteral (lumbar ureter vs pelvic ureter) or pelvic location was possible. Finally, all the limitations related to the retrospective nature of the SEER database apply to this, as well as all other SEER database or population-based analyses.

Conclusions

LNI in non-metastatic UTUC patients is the most important determinant of CSM. Number of positive lymph node is independently associated with higher CSM. In consequence, lymph node dissection can provide extensive prognostic information.

Author contributions

Sebastiano Nazzani and Zhe Tian had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial disclosures

Sebastiano Nazzani certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

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Conflict of interest

None to declare.

Ethical approval

Not necessary.

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Appendix A. Supplementary data

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