

No overt influence of lymphadenectomy on cancer-specific survival in organ-confined versus locally advanced upper urinary tract urothelial carcinoma undergoing radical nephroureterectomy: a retrospective international, multi-institutional study

Maximilian Burger · Shahrokh F. Shariat · Hans-Martin Fritsche · Juan Ignacio Martinez-Salamanca · Kazumasa Matsumoto · Thomas F. Chromecki · Vincenzo Ficarra · Wassim Kassouf · Christian Seitz · Armin Pycha · Stefan Tritschler · Thomas J. Walton · Giacomo Novara

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Abstract

Purpose Lymph node dissection (LND) is not routinely performed during radical nephroureterectomy (RNU) in upper tract urothelial carcinomas (UTUC), and its clinical relevance is unclear. The purpose of the present study was to evaluate the impact of LND on clinical outcomes in a large multicenter series of RNU for UTUC.

Methods Detailed data on 785 patients subject to RNU were provided by nine international academic centers. The choice to perform lymphadenectomy was determined by the treating surgeon. All pathology slides were evaluated by dedicated genitourinary pathologists. Univariable and multivariable Cox regression models evaluated the association of nodal status with recurrence-free (RFS) and cancer-specific (CSS) survival.

Results One hundred and ninety patients had LND. Pathological N stage was pN0 in 17%, pNx in 76%, and pN+ in 7%. The median follow-up period of the entire cohort was

34 months (interquartile range [IQR]: 15–65 months). Overall, five-year RFS and CSS estimates were 72.2 and 76%, respectively. In multivariable Cox regression analyses, pN0/pNx substaging was not an independent predictor of either RFS (hazard ratio [HR]: 1.1; $P = 0.631$) or CSS (HR: 1.3; $P = 0.223$). Similar results were obtained in a subgroup analysis limited to patients with organ-confined disease (HR: 0.9; $P = 0.907$ for RFS; HR: 0.4; $P = 0.419$ for CSS). Conversely, in patients with locally advanced disease, patients with pN0 disease have significantly better cancer-related outcomes (HR: 0.3; $P < 0.001$ for RFS; HR: 0.3; $P < 0.001$ for CSS).

Conclusion The present series suggests pNx is more significantly associated with a worse prognosis than pN0, but only in patients with locally advanced UTUC.

Keywords Lymph node · Nephroureterectomy · Survival · Urothelial carcinoma · Lymphadenectomy

M. Burger (✉) · H.-M. Fritsche
Department of Urology, Caritas St. Josef Medical Centre,
University of Regensburg, Landshuterstr.
65, 93053 Regensburg, Germany
e-mail: maximilian.burger@klinik.uni-regensburg.de

S. F. Shariat · T. F. Chromecki
Weill Medical College of Cornell University,
New York, NY, USA

J. I. Martinez-Salamanca
Hospital Universitario Puerta de Hierro-Majadahonda,
Universidad Autónoma de Madrid, Madrid, Spain

K. Matsumoto
Kitasato University School of Medicine,
Sagamihara, Kanagawa, Japan

V. Ficarra · G. Novara
University of Padua, Padua, Italy

W. Kassouf
McGill University Health Centre, Montréal, QC, Canada

C. Seitz · A. Pycha
General Hospital Bolzano, Bolzano, Italy

S. Tritschler
Department of Urology, Ludwig-Maximilians-University,
Munich, Germany

T. J. Walton
Derby City General Hospital, Derby, UK

Abbreviations

UTUC	Upper tract urothelial carcinoma
RNU	Radical nephroureterectomy
LND	Lymph node dissection
RCT	Randomized controlled trials
LVI	Lymphovascular invasion
RFS	Recurrence-free survival
CSS	Cancer-specific survival
IQR	Interquartile range
SE	Standard error
HR	Hazard ratio

Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease accounting for roughly 5% of all urothelial cancers [1]. Although selected patients with small well-differentiated tumors may be amenable to a nephron-sparing surgery through endourologic approaches, radical nephroureterectomy (RNU) with bladder cuff resection and regional lymphadenectomy is the mainstay of treatment [2–4]. While lymph node dissection (LND) is an obligatory part of radical cystectomy to improve staging [5] and, according to some, also survival [6–9], it is not unanimously performed in UTUC. The presence of positive lymph nodes and number of positive nodes are currently regarded as major prognostic factors in UTUC [10–15]; however, the impact of LND on survival is unclear. Specifically, some small, single-institution studies have suggested that an extended lymphadenectomy may provide a survival benefit in UTUC patients treated with RNU [16–18]. More recently, a large report from the first UTUC collaboration suggested that patients with pN0 disease had better cancer-specific survival than those with pNx disease, but only in cases of pathological T stage higher or equal to T2, whereas the pN0/pNx substaging failed to be an independent predictor of CSS in pT1 UTUC [19]. Conversely, in a large population-based study collecting more than 2,800 patients treated from 1988 to 2004 and included in the SEER database, Lughezzani et al. failed to demonstrate a statistically significant difference in CSS of pN0 and pNx patients [20].

Due to the controversies about the available literature and also to the lack of randomized controlled trials (RCTs) addressing such issues, a large and independent multicenter cohort of patients who underwent RNU for UTUC were examined to evaluate the prognostic role of pN0/pNx.

Patients and methods

This was an institutional review board–approved study, with all participating sites providing the necessary institutional

data-sharing agreements before initiation of the study. A total of 9 international academic 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 the final analysis, the database was frozen, and the final data set was produced for the current analysis.

The database was comprised of 785 patients who had undergone RNU with ipsilateral bladder cuff resection between 1987 and 2008, all of which were subjects for the current analysis.

Surgery was performed by several surgeons according to standard criteria for RNU (i.e., extrafascial dissection of kidney with the entire length of ureter and adjacent segment of bladder cuff). Hilar and regional lymph nodes adjacent to ipsilateral great vessel were generally resected at the discretion of the treating physician. An extended lymphadenectomy was not routinely performed.

Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at the respective institutions. Tumors were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification [21]. Tumor grading was assessed according to the 1973 WHO/International Society of Urologic Pathology consensus classification [22]. Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls.

Follow-up regimen

Patients were generally observed every 3–6 months for the first year after RNU, every 6 months from the second through the fifth years, and annually thereafter. The follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scan, chest computed tomography, and magnetic resonance imaging were performed when clinically indicated.

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Bladder recurrences were not considered in the analysis of the recurrence-free survival (RFS) rate. Cause of death was determined by the treating physician, by chart review corroborated by death certificates, or by death certificates

Table 1 Association of N stage with clinical and pathologic characteristics of 785 patients treated with radical nephroureterectomy and bladder cuff excision for upper tract urothelial carcinoma

	Cases (%)	Lymph node stage			P value
		pN0 (n = 136, 17%)	pNx (n = 595, 76%)	pN1/2 (n = 54, 7%)	
Age (years; median and IQR)	68 (61–75)	64.9 (58.3–72.1)	69 (61.8–75)	68 (63.3–76)	0.002
Gender					
Male	542 (69%)	101 (19%)	399 (74%)	42 (7%)	0.093
Female	243 (31%)	35 (14%)	196 (81%)	12 (5%)	
Type of surgery					
Open RNU	715 (91%)	117 (16%)	546 (77%)	52 (7%)	0.134
Laparoscopic RNU	70 (9%)	19 (27%)	49 (70%)	2 (3%)	
Pathologic stage					0.007
pTa	165 (21%)	22 (13%)	141 (86%)	2 (1%)	
pTis	10 (1%)	1 (10%)	9 (90%)	0	
pT1	196 (25%)	32 (16%)	163 (83%)	1 (1%)	
pT2	148 (19%)	34 (23%)	111 (75%)	3 (2%)	
pT3	222 (28%)	41 (18%)	152 (69%)	29 (13%)	
pT4	44 (6%)	6 (14%)	18 (43%)	19 (43%)	
Grade					
G1	100 (13%)	18 (18%)	81 (81%)	1 (1%)	<0.001
G2	226 (29%)	21 (9%)	200 (89%)	5 (2%)	
G3	459 (58%)	97 (21%)	314 (68%)	48 (11%)	
Number of removed lymph nodes median and IQR)	3 (2–6)	3 (2–6)	–	2 (2–4)	NA
Lymphovascular invasion*					
Absent	620 (79%)	100 (16%)	494 (80%)	26 (4%)	<0.001
Present	152 (19%)	32 (21%)	93 (61%)	27 (18%)	
Concomitant carcinoma in situ					
Absent	689 (88%)	118 (17%)	527 (77%)	44 (6%)	0.290
Present	96 (12%)	18 (19%)	68 (71%)	10 (10%)	
Adjuvant chemotherapy					
Administered	69 (9%)	13 (19%)	27 (39%)	29 (42%)	<0.001
Not administered	716 (91%)	123 (17%)	568 (79%)	25 (4%)	
Follow-up duration (median and IQR)	34 (15–65)	28.5 (12–78.7)	37 (17–66)	14.5 (8.7–26.5)	<0.001

IQR interquartile range; RNU radical nephroureterectomy

* missing in 13 cases

alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (i.e., death within 30 days of surgery) were censored at time of death for cancer-specific survival (CSS) analyses.

Statistical analysis

The Fisher's exact test and the chi-square (χ^2) test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Kruskal–Wallis test. The Kaplan–Meier method was

used to calculate survival functions, and differences were assessed with the log rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as $P \leq 0.05$. All reported P values are two-sided. Analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

Results

One hundred and ninety patients had lymph node dissections, yielding a median number of 3 (interquartile range

[IQR]: 2–6) nodes. More than 10 nodes were obtained only in 12% of the cases. Pathological N stage was N0 in 136 (17%), pNx in 595 (76%), and pN+ in 54 (7%). Table 1 summarizes the association of N stage with clinical and pathologic characteristics of the 785 evaluated patients. Age, pathological T stage, tumor grade, prevalence of LVI, use of adjuvant chemotherapy, and follow-up duration were all significantly different across the 3 subgroups (all P values <0.002) (Table 1). No patient received neoadjuvant chemotherapy.

The median follow-up period of the entire cohort was 34 months (IQR: 15–65 months). At the last follow-up, 190 patients (24%) had developed disease recurrence and 162 (21%) had died of UTUC. Moreover, 103 patients (13%) experienced non-cancer-related deaths. The median follow-up for the 455 patients alive at the last follow-up was 42 months (IQR: 19–77 months).

The overall two- and five-year RFS estimates were 78.7% (standard error [SE]: 1.6%) and 72.2% (SE: 1.8%), respectively. The overall two- and five-year CSS estimates were 81.4% (SE: 1.2%) and 76% (SE: 1.7%), respectively.

Pathological N stage was significantly associated with an increased risk of disease recurrence and cancer-specific death. Specifically, the five-year RFS estimates were 71.6% (SE: 4.8%), 76.9% (SE: 2.0%), and 21.3% (SE: 6.3%), for pN0, pNx, and pN1/2 tumors, respectively (Fig. 1; log rank pooled over strata $P < 0.001$; pN0 versus pNx: $P = 0.586$; pN0 versus pN1/2: $P < 0.001$; pNx versus pN1/2: $P < 0.001$). Similarly, the five-year CSS estimates were 79% (SE: 4.3%), 77.4% (SE: 4.6%), and 26.7% (SE: 6.9%), for pN0, pNx, and pN1/2 tumors, respectively (Fig. 2; log rank pooled over strata $P < 0.001$; pN0 versus pNx: $P = 0.945$; pN0 versus pN1/2: $P < 0.001$; pNx versus pN1/2: $P < 0.001$).

Tables 2 and 3 summarize univariable and multivariable analysis for RFS and CSS, respectively. In univariable analysis, pN0/pNx substaging was not significantly associated with an increased risk of disease recurrence (hazard rate [HR]: 0.9; $P = 0.585$) or cancer-related death (HR: 1.0; $P = 0.962$). In multivariable Cox regression analyses that included age, gender, surgical type, T stage, grade, presence of concomitant CIS, and presence of lymphovascular invasion, pN0/pNx substaging was not found to be an independent predictor of either RFS (HR: 1.1; $P = 0.631$) or CSS (HR: 1.3; $P = 0.223$).

Similar results were obtained in subgroup analyses limited to patients with organ-confined disease (HR: 0.9; $P = 0.907$ for RFS; HR: 0.4; $P = 0.419$ for CSS; Fig. 3). Conversely, in locally advanced disease, patients with pN0 disease have a significantly lower risk of recurrence (HR: 0.3; $P < 0.001$; Fig. 4) and death (HR: 0.3; $P < 0.001$), when compared to pNx disease, once adjusted for the effect of age, gender, type of surgery, presence of LVI, and concomitant CIS.

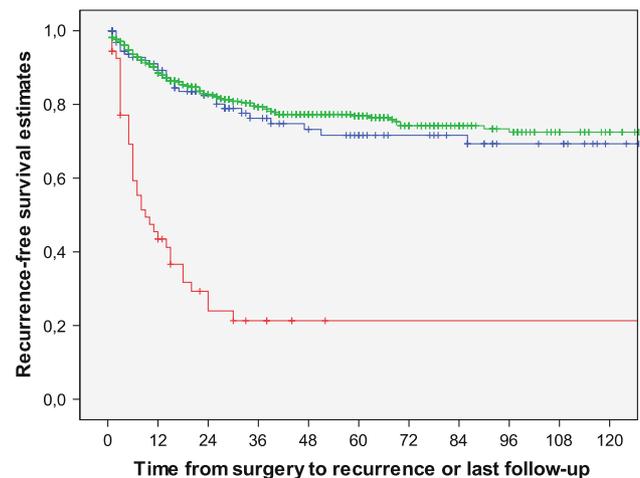


Fig. 1 Kaplan–Meier curves of recurrence-free survival stratified by lymph node stage in 785 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma. Blue curve patients with pN0 tumors; green curve patients with pNx tumors; red curve patients with pN1/2 tumors. Log rank pooled over strata $P < 0.001$; pN0 versus pNx: $P = 0.586$; pN0 versus pN1/2: $P < 0.001$; pNx versus pN1/2: $P < 0.001$

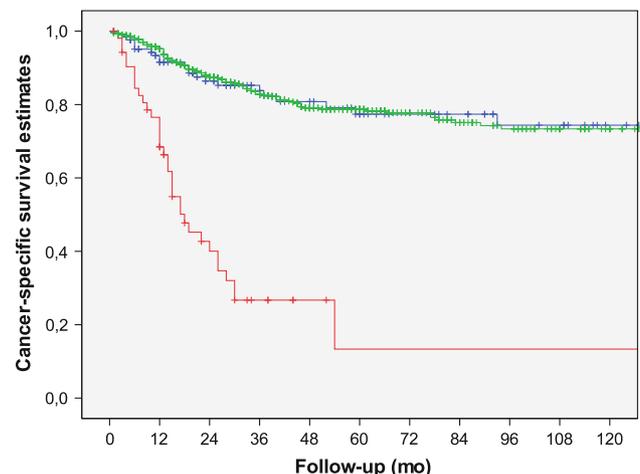


Fig. 2 Kaplan–Meier curves of cancer-specific survival stratified by lymph node stage in 785 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma. Blue curve patients with pN0 tumors; green curve patients with pNx tumors; red curve patients with pN1/2 tumors. Log rank pooled over strata $P < 0.001$; pN0 versus pNx: $P = 0.960$; pN0 versus pN1/2: $P < 0.001$; pNx versus pN1/2: $P < 0.001$

Discussion

The current study found that patients who did not receive any LND during RNU for UTUC had worse cancer-related outcome compared to those with pN0 disease only in case of pathologically locally advanced disease. Conversely,

Table 2 Univariable and multivariable Cox regression analyses for the prediction of disease recurrence in 785 patients treated with RNU ipsilateral bladder cuff excision for UTUC (190 recurrences)

Parameter	Univariable analysis			Multivariable analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age	1.02	1.0–1.03	0.015	1.02	1.0–1.03	0.042
Gender	0.9	0.7–1.3	0.610	0.9	0.7–1.2	0.539
Type of surgery	1.4	0.9–2.3	0.166	1.2	0.7–2.0	0.461
Pathologic stage			<0.0001			<0.0001
pTa/Tis	1	Reference	–	1	Reference	–
pT1	1.3	0.6–2.4	0.513	1.1	0.5–2.1	0.848
pT2	3.1	1.7–5.7	<0.0001	2.3	1.2–4.6	0.011
pT3	6.2	3.6–10.8	<0.0001	3.7	2.0–6.8	<0.0001
pT4	35.1	18.8–65.6	<0.0001	14.4	6.7–30.9	<0.0001
Grade			<0.0001			0.063
G1	1	Reference	–	1	Reference	–
G2	2.2	0.9–5.2	0.082	1.6	0.7–4.1	0.284
G3	6.8	3.0–15.4	<0.0001	2.4	0.9–5.7	0.055
Concomitant CIS	2.0	1.4–3.0	<0.0001	1.6	1.1–2.4	0.013
Lymphovascular invasion	3.9	2.8–5.2	<0.0001	1.6	1.2–2.3	0.003
Lymph node stage			<0.0001			0.012
pN0	1	Referent	–	1	Referent	–
pNx	0.9	0.6–1.3	0.585	1.1	0.7–1.7	0.631
pN1/2	5.8	3.5–9.4	<0.0001	2.0	1.2–3.4	0.009

UTUC upper tract urothelial carcinoma; HR hazard ratio; CI confidence interval; CIS carcinoma in situ

omitting LND during RNU does not jeopardize the outcome of those patients with pathologically localized UTUC.

Although LND is an established part of a radical cystectomy for bladder cancer [5], its necessity is debated in RNU for UTUC. Although presence of positive lymph nodes and number of positive nodes are currently regarded as major prognostic factor in UTUC [10–15], the impact of LND on survival is unclear. Specifically, some small, single-institution studies have suggested that lymphadenectomy may provide a survival benefit in UTUC patients treated with RNU [16–18]. More recently, a large report of the first UTUC collaboration involving more than 1,100 patients suggested that patients with pN0 disease had better RFS (HR: 1.4; $P = 0.018$) and CSS (HR: 1.4; $P = 0.016$) than those with pNx disease in case of pathological T stage higher or equal to T2, whereas the pN0/pNx substaging failed to be an independent predictor of cancer-related outcomes in pT1 UTUC [19]. Conversely, in a large population-based study collecting more than 2,800 patients treated from 1988 to 2004 and included in the SEER database, Lughezzani et al. did not demonstrate any statistically significant differences in CSS of pN0 and pNx patients

(81.2 vs. 77.8%, respectively), with pN0 versus pNx status failing to be statistically significant both in univariable (HR: 1.2; $P = 0.09$) and in multivariable analyses (HR: 0.99; $P = 0.9$) [20]. The results of the current study suggest that patients who did not receive any LND have no better prognosis than patients who undergo an LND without pathologically proven lymph node metastases, which echoes the data of the Lughezzani's paper, despite the fact that the prevalence of LNDs in our series was significantly lower (24% vs. 75% in the SEER report). However, in subgroup analyses limited to patients with pathologically locally advanced disease, we found that patients with pN0 disease had a better prognosis compared with those with pNx disease, which was similar to what was previously reported in the reports of the first UTUC collaboration [14, 19]. Notably, in both series, the extension of LND was not very wide, as reflected by the median number of removed nodes (3 in the present series vs. 5 in the Roscigno's study) [14].

Taken together, these data suggest that LND might be of benefit in those patients who are expected to harbor locally advanced disease. Unfortunately, to date, there is a lack of validated predictive tools to estimate the patholog-

Table 3 Univariable and multivariable Cox regression analyses for the prediction of cancer-specific mortality in 785 patients treated with RNU ipsilateral bladder cuff excision for UTUC (162 cancer-specific deaths)

Parameter	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.02	1.01–1.04	0.005	1.02	1.01–1.04	0.005
Gender	0.8	0.6–1.1	0.216	0.8	0.6–1.1	0.177
Type of surgery	0.9	0.5–1.8	0.835	0.8	0.4–1.6	0.531
Pathologic stage			<0.0001			<0.0001
pTa/Tis	1	Reference	–	1	Reference	–
pT1	1.3	0.6–2.7	0.536	1.2	0.5–2.6	0.709
pT2	3.3	1.7–6.7	0.0001	2.7	1.2–6.0	0.012
pT3	7.8	4.2–14.8	<0.0001	5.1	2.4–10.7	<0.0001
pT4	46.7	23.1–94.5	<0.0001	21.6	8.9–51.9	<0.0001
Grade			<0.0001			0.221
G1	1	Reference	–	1	Reference	–
G2	1.7	0.7–4.2	0.239	1.2	0.5–3.0	0.727
G3	5.7	2.5–13.0	<0.0001	1.7	0.7–4.2	0.253
Concomitant CIS	1.9	1.3–2.8	0.001	1.5	0.9–2.3	0.062
Lymphovascular invasion	4.5	3.3–6.2	<0.0001	1.8	1.3–2.6	0.001
Lymph node stage			<0.0001			0.053
pN0	1	Referent	–	1	Referent	–
pNx	1.0	0.6–1.6	0.962	1.3	0.8–2.2	0.223
pN1/2	6.7	3.9–11.6	<0.0001	2.1	1.1–3.8	0.017

RNU radical nephroureterectomy; UTUC upper tract urothelial carcinoma; HR hazard ratio; CI confidence interval; CIS carcinoma in situ

ical stage of UTUC at RNU. Specifically, Margulis et al. recently reported a simple nomogram including only tumor grade, architecture, and location able to predict probability of non-organ-confined disease with a 79% accuracy [23]. However, that tool has not been validated yet, and no such attempt has currently been initiated to our knowledge.

There are several limitations to this study. First and foremost are the limitations inherent to retrospective analyses. Although multiple internal and external reviews of the consortium data set have been conducted, patients were excluded from this analysis for whom complete information could not be obtained, which could possibly create selection bias. No stringent and concise data on clinical staging allowing statistical evaluation of impact on decision for LND or on occurrences of bladder tumors were available. In addition, the population in this study underwent RNU by multiple surgeons, indication and extension of lymph node dissection were not standardized, and specimens were evaluated by multiple pathologists without slide review. The LND template was not defined, and overall numbers per center and surgeon are still low. However, all surgeons operated at selected

centers with significant experience in urothelial cancer management, and all specimens were examined by dedicated genitourinary pathologists at selected centers. Finally, study design did not allow for the exclusion of biases such as the Will Rogers phenomenon, which could play a major role in all non-randomized comparisons [24]. However, a RCT is unlikely to be performed due to the relatively low prevalence of UTUC, and most clinical questions on this entity have been answered in retrospect to date [25, 26].

Conclusions

Although the present series cannot provide a definite evaluation of the benefit of LND during RNU, it does suggest two aspects. Patients who did not receive any LND during RNU for UTUC had worse cancer-related outcomes compared with those with pN0 disease, but only in cases of pathologically locally advanced disease. And conversely omitting LND during RNU does not jeopardize the outcome of those patients with pathologically localized UTUC.

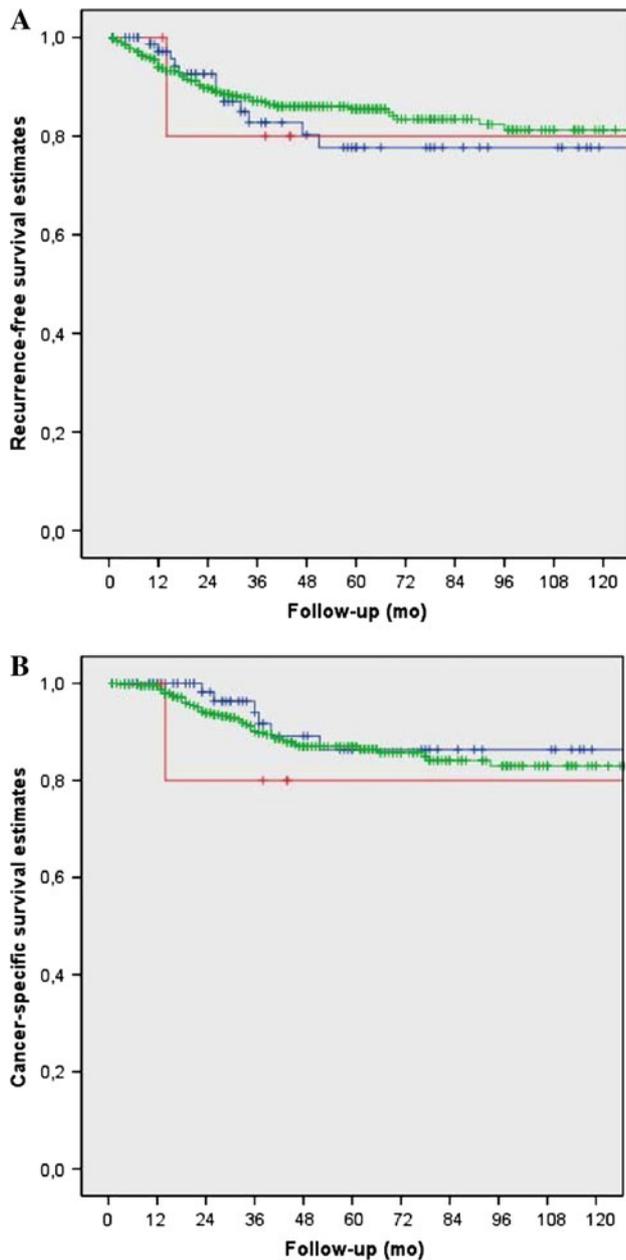


Fig. 3 Kaplan–Meier curves of recurrence-free survival (a), and cancer-specific survival (b) stratified by lymph node stage in 519 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for organ-confined upper tract urothelial carcinoma. *Blue curve* patients with pN0 tumors; *green curve* patients with pNx tumors; *red curve* patients with pN1/2 tumors. Log rank pooled over strata for **a** and **b**: $P = n.s.$; pN0 versus pNx: $P = n.s.$; pN0 versus pN1/2: $P = n.s.$; pNx versus pN1/2: $P = n.s.$

Conflict of interest All authors declare that there are no conflicts of interest.

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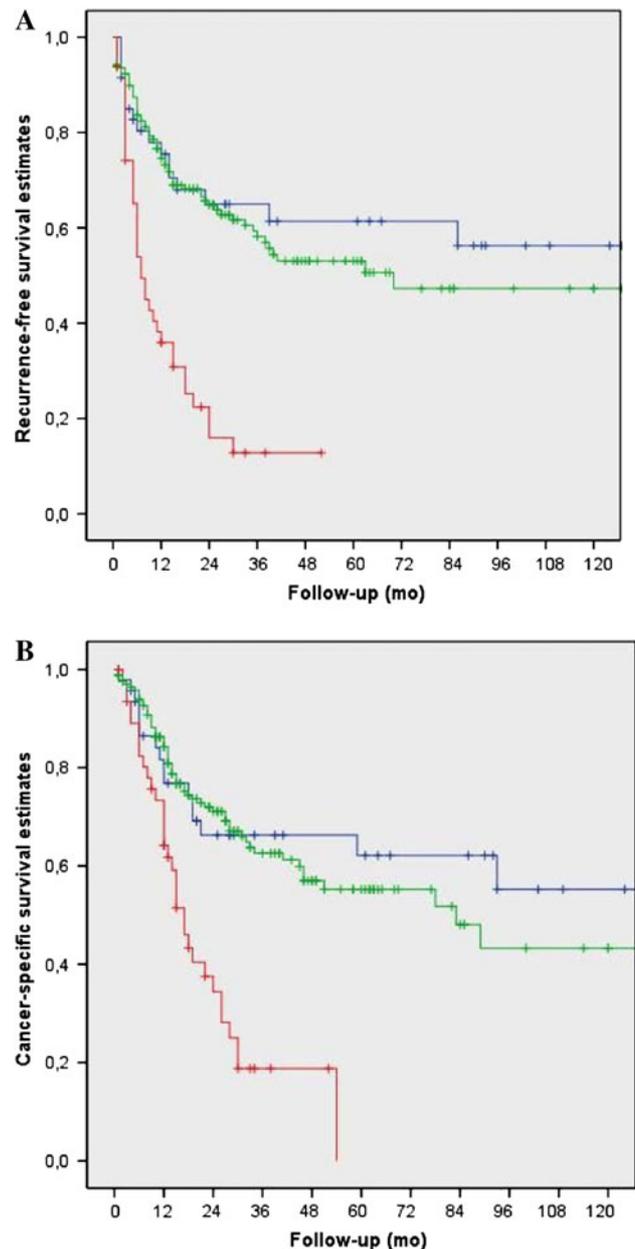


Fig. 4 Kaplan–Meier curves of recurrence-free (a), and cancer-specific survival stratified by lymph node stage in 266 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for locally advanced upper tract urothelial carcinoma. *Blue curve* patients with pN0 tumors; *green curve* patients with pNx tumors; *red curve* patients with pN1/2 tumors. Log rank pooled over strata **a**: pN0 versus pNx: $P = 0.578$; pN0 versus pN1/2: $P < 0.001$; pNx versus pN1/2: $P < 0.001$. **b**: pN0 versus pNx: $P = 0.633$; pN0 versus pN1/2: $P < 0.001$; pNx versus pN1/2: $P < 0.001$

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