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Clinicopathological prognostic factors for upper tract urothelial carcinoma

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Introduction The aim of the present study was to evaluate the influence of clinicopathological factors including age, gender, tumor grade, tumor stage, lymphovascular invasion (LVI), tumor necrosis and previous history of non-muscle invasive bladder cancer on outcomes of patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy (RNU).
Material and methods A total of 60 patients who underwent radical nephroureterectomy for upper tract urothelial carcinoma at our institute between 2005 to 2012 were included in our study. Univariate and multivariate analysis was performed using the Kaplan-Meier method, log rank statistics, the chi-square test and Cox regression models.
Results The mean length of follow-up time was 33.3 months. There were 27 (45%) patients alive with the disease, whereas 33 (55%) were dead. In 19 cases (31.7%) the tumor grade was low, while in 41 cases (68.3%) it was high. Lymphovascular invasion was observed in 28 (46.7%) cases. Tumor necrosis was registered in 14 patients (23.3%). From the patients with LVI, 3 (9.6%) were alive, whereas from the patients negative for LVI, 75% were alive. Significant relationship was found between gender and grading and between positive LVI and low grading.
Conclusions Day case Variables such as gender, grading, tumor stage, LVI and tumor necrosis were all demonstrated to be significant independent prognostic factors for the overall survival. On the multivariate analysis only LVI remained statistically significant, which may explain the different clinical course in patients and could be considered as a part of pathological reporting and treatment planning for the future.

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INTRODUCTION

Upper urothelial tract carcinomas (UTUC) are rare tumors that account for about 5% of genitourinary malignancies [1]. Despite the introduction of minimally invasive techniques and the revisions in some of the indications for radical surgery, especially for low risk patients, radical nephroureterectomy (RNU) with bladder cuff excision remains the surgical standard of care for patients with non-metastatic UTUC. It is also the only one graded with the level of recommendation A in the revised and updated issues of the guidelines of the European Association of Urology [2].

Tumor necrosis, advanced stage, lymphovascular invasion, hydronephrosis, tumor size and location have all been identified as prognostic factors for the overall and cancer specific survival [3, 4]. Despite the accumulating data, the need for establishing new and reliable prognostic factors may play a bigger role in the near future for establishing recommendations for the stringent follow -up and treatment after RNU for UTUC.
The aim of the present study was to evaluate the influence of clinicopathological factors including age, gender, tumor grade, tumor stage, lymphovascular invasion (LVI), tumor necrosis and previous history

of non-muscle invasive bladder cancer on cancer specific survival (CSS) and overall survival (OS).

MATERIAL AND METHODS

A retrospective analysis was conducted for the patients who underwent RNU for UTUC at our institute during the time period of 2005 to 2012. Inclusion criteria were urothelial carcinoma of pyelocaliceal system or ureter. Cases of UTUC with concomitant or previous history of non-muscle invasive urothelial carcinoma of the bladder were also included in our study. Exclusion criteria was muscle-invasive carcinoma of the bladder, or distant metastasis. Since one of our aims was to evaluate the effect of LVI invasion, positive lymph nodes were also included as exclusion criteria. RNU was performed using a standardized open technique with lumbar and Gibson incision for optimal access both to both the kidney and proximal ureter and to the distal ureter and bladder, respectively. The bladder cuff was excised with a radius of at least 1.5 cm around ureteral insertion. Lymph node dissection was performed when positive lymph nodes were suspected. Surgical specimens were examined by three experienced genitourinary pathologists applying standardized protocol. The specimens were fixed in formalin, embedded in paraffin and stained with H&E. Tumor grading was standardized according to the 2004 WHO grading system distinguishing between papillary urothelial neoplasm of low malignant potential (PUNLMP) and low and high grade urothelial carcinoma. The surgical specimens were assessed for the depth of tumor invasion, LVI, size of tumor (measured in the surgical specimen) and necrosis of more than 10% of the tumor area. The follow- up was standardized for all patients. Urine cytology and cystoscopy were performed at the 3 month and 9 month follow-up and if no relapse was observed, procedures were performed annually. Computer tomography scans were performed at the 6 month and 12 month follow-up and then afterwards annually.

Statistical analysis was performed to assess the prognostic effect of age, gender, tumor grade, tumor stage, lymphovascular invasion (LVI), tumor necrosis and previous history of non-muscle invasive bladder cancer on cancer specific survival (CSS) and overall survival (OS) among patients treated for UTUC. Univariate analysis was performed using the Kaplan-Meier method and log rank statistics. The chi -square test was used to test for correlations between the variables. Multivariate analysis was performed using Cox regression models. All statistical analyses were performed with SPSS v. 19 at 5% risk level (p <0.05).

RESULTS

A total of 63 patients underwent RNU for UTUC at our institute from the period 2005–2012. One patient was verified with adenocarcinoma of the renal pelvis and was excluded from the study. Another two patients were excluded – one of them had positive lymph nodes, whereas the other underwent RNU with cystoprostatectomy for concomitant muscle-invasive carcinoma of the bladder. A total of 60 patients fulfilled the inclusion criteria and were included in the study.

The mean length of follow-up time was 33.3 months with range from 1 to 84 months. Of the 60 patients 32 (53.3%) were under 65 years, whereas 28 (46.6%) where 65 years or over. At the time of our analysis 27 (45%) patients were alive, whereas 33 (55%) were dead. The 1-year, 3-year and 5-year survival rates were 61.7%, 48.4%, and 38.8%, respectively. Accurate cause-specific morality data of our subjects was available only for the first 12 months of our study. From the 19 deceased at the end of the first year, cancer – related death was proven for the 16 of them. The other three patients died from non-cancer related reasons (pulmonary embolism, myocardial infarction, and no data for the third patient). Hence, accurate cancer specific survival analyses could be performed only for the first year following RNU, which is 73.4%. Unfortunately, in the following years the drop-off rate of the patients would reach up to 45% by the fifth year. At the end of the study, after evaluating the documents from the follow-up, we discovered that 27 patients dropped out due to unknown reasons. Most of them dropped out of the study between the third and fifth year (20 patients). The drop out rate for the third year was 11.6%. Survival data for these patients was collected from available national and health data registries. For 4 patients not enough sufficient information was gathered regarding the treatment process or follow-up and they were excluded from the survival analysis. 17 of the patients (28.33%) had concomitant or a history of non-muscle invasive bladder cancer at time of diagnosis, treated with transurethral resection. 8 patients (13.3 %) suffered bladder recurrence. For 6 of them (75%) this was observed in the first 12 months after surgery.

The tumor location was the pyelocaliceal system for 57 cases (95%) and the ureter in 3 (5%). Due to the limited amount of patients no statistical analyses could be performed to assess the effect of tumor location on the outcomes.
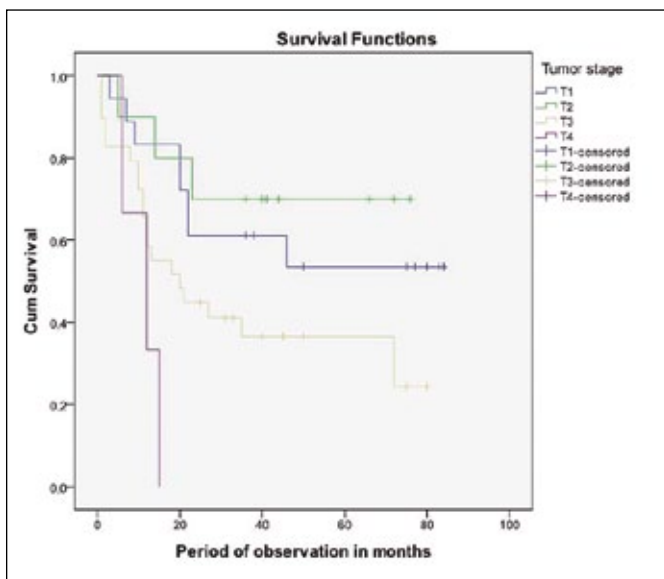
Sufficient data for tumor size was available for only 34 of the patients. Despite the small amount of patients, we decided to investigate this group separate-
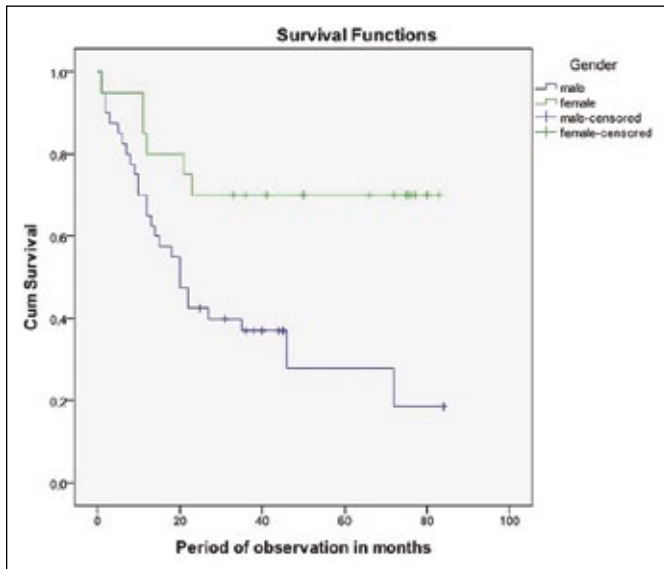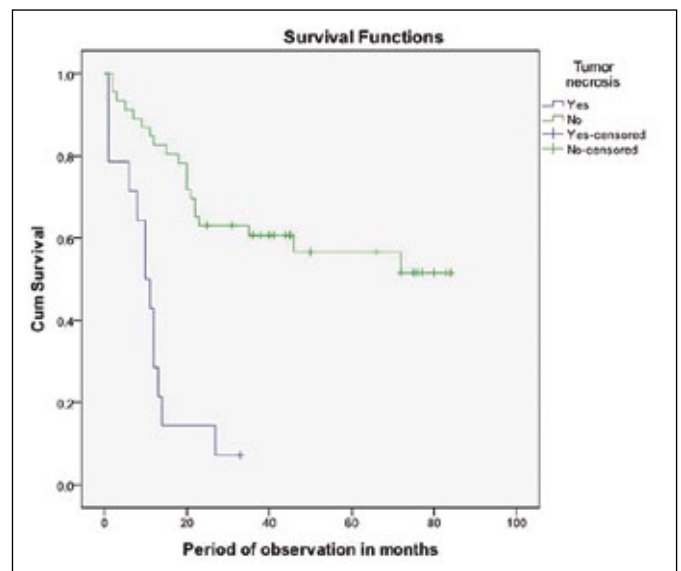
Figure 1. Kaplan-Meier curves of overall survival stratified according to gender.
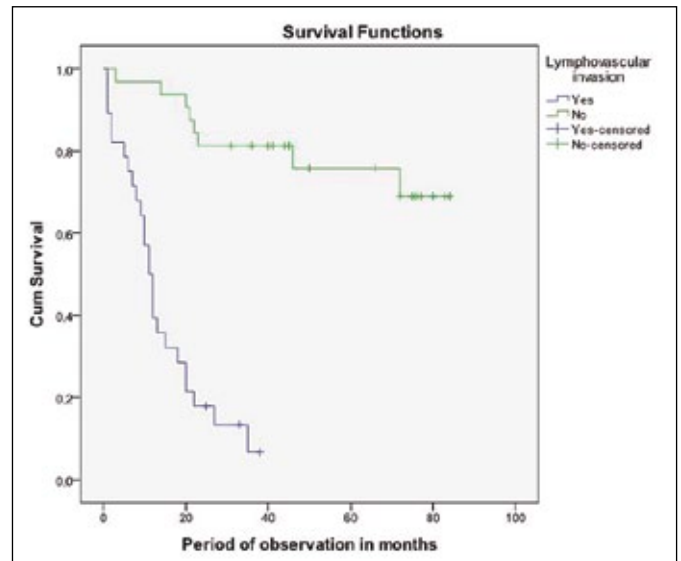
Figure 3. Kaplan-Meier curves of overall survival stratified according to lymphovascular invasion.

Figure 2. Kaplan-Meier curves of overall survival stratified according to tumor stage.

Figure 4. Kaplan-Meier curves of overall survival stratified according to tumor necrosis.

ly from the others and to evaluate the effect of the variable on survival outcomes. Our analysis showed that the larger tumor size had a negative effect on survival (p = 0.018), but the small number of observations did not allow us to state this with the desired confidence.

On the univariate analysis, variables such as gender (Figure 1), grading, tumor stage (Figure 2), LVI (Figure 3) and tumor necrosis (Figure 4) were all demonstrated to be significant prognostic factors affecting OS and CSS (Table 1). On the other hand,

on the multivariate analysis only LVI remained statistically significant (p- value <0.001. HR = 11.089, 95% CI: lower bound – 4.418, upper bound – 27.835). A statistically significant relationship was found between gender and grading. There were 77.5% of males that were high-grade, whereas for females this percent was 50% (p = 0.031). No PUNLMP was observed in our series. In the presented study, LVI was also significantly associated with high grading (p <0.001). The analysis showed a negative relationship between tumor necrosis and age. Tumor

Table 1. *Univariate analysis for overall survival*

Clinicopathological variable	Category	N(%)	OS (%)	p-values
Age	>65 <65	28 (46.67%) 32 (53.33%)	40% 49%	0.832
Gender	M F	40 (66.67%) 20 (33.33%)	32.5% 70%	0.006
Grading	Low grade High grade	19 (31,67%) 41 (68,33%)	100% 19.5%	<0.001
Tumor stage	T1 T2 T3 T4	18 (30%) 10 (17%) 29 (48%) 3 (5%)	55.9% 70% 34.6% 0%	0.016
LVI	Yes No	28 (46.67%) 32 (53.33%)	9.6% 75%	<0.001
Tumor necrosis	Present Absent	14 (23.33%) 46 (76.67%)	7.1% 56.5%	<0.001
Concomitant/History of Bladder carcinoma	Yes No	17 (28.33%) 43 (71.67%)	41.1% 46.5%	0.584
Tumor size	>3 cm <3 cm	12 (35.3%) 22 (64.7%)	75% 22.7%	0.018

necrosis was observed in 52.4% of the patients aged 65 years or less and in 10.7% of the patients above 65 years of age (p = 0.031). Tumor necrosis was associated with high grading (p = 0.004) and LVI (p <0.001).

DISCUSSION

The amount of studies regarding the effect of age in patients with UTUC is relatively limited (5). Shariat et al. reported that in a series of 1,453 patients, being older at the time of RNU, there was an associated decrease in survival. This was attributed to a change in the biological potential of the tumor cell, a decrease in the host's defense mechanisms, or differences in care patterns. However, advanced age alone should not be regarded as exclusion criteria and many elderly patients might be cured with RNU [2, 5] In our study the percentage of patients over and under 65 years of age were 46.6% and 53.3%, respectively. By the end of our study 60 % of patients over 65 years were dead , while for patient under 65 this percent was 51%. No statistical relationship was found between the age and OS (p = 0.83).

The effect of gender was investigated in a number of studies [6, 7]. Lughezzani et.al. compared 2,903 (59.9%) males and 1,947 (40.1%) females who underwent RNU for pT(1-3)N(0/x)M(0) UTUC. It was reported that females were more likely to have a more advanced pathologic T stage and higher tumor grade

at the time of RNU than males. However, on multivariate analysis accounting for stage, grade, and noncancerous characteristics, gender was no longer found to affect cancer specific survival and OS. In the study of Shariat et al. consisting of 754 patients treated with RNU for UTUC, male gender was found to correlate with higher grading and similarly to the other mentioned study, it had no effect on cancer specific survival and overall survival [7]. In addition, our study noted a positive correlation between female gender and low grading (p = 0.031) which was consistent with the literature [6, 7]. Male patients were 66.67% in our study and this gender ratio was also consistent with literature [7]. In our study, the male gender was found to be a negative prognostic factor for OS (p = 0.006), which did not correlate with the available data, but could be attributed to the small number of patients in our study and to the fact that low grade was found to have a positive effect on OS (p <0.001).

According to 2004 WHO classification, tumor grading is divided into papillary urothelial neoplasia of low malignant potential, high grade and low-grade carcinomas. Until 2004, the most commonly used grading system was 1974 WHO system where three grades were used. Some of the more recent series used the two-piered system and found that low grade was a strong independent prognostic factor for better outcome in patients with UTUC that were treated with RNU [23, 24, 25]. In our study a significant relationship was established between tumor grading and OS. (p <0.001). All of the low grade patients were alive by the end of the study, whereas for the high grade patients the OS rate was 19.5%.

In previous studies tumor staging has been found to be an important prognostic factor for patients with UTUC. In most of the largest series, tumor stage was found to be a prognostic indicator [7, 8, 9, 29]. With the advancing progression of the malignancy, urothelial carcinoma can spread by direct invasion, mucosal seeding, hematogenic and lymphatic routes. Patients with pT1 are found to have a cancer specific survival >90%, whereas for stage T3–T4 it is 40.5% and 19%, respectively [29]. In our study, the 3-year and 5-year survival rates were 48.4%, and 38.8%, respectively. The results were worse than what was most often reported in literature [29, 31]. We can attribute this to the high prevalence of invasive stage disease (>T2) in our series – 70%. In the literature the muscle invasive stage, in most of the series, has been estimated to be 18–48% [31]. In some studies, the OS and CSS have been reported to be less than 50% for stage T2 and higher [32]. The late stage at which the patients are diagnosed and treated is a problem

which must not be underestimated by physicians. Our statistical analyses revealed that the stage of the tumor has a negative effect on OS (p = 0.016). Significant amount of studies show LVI as an important prognostic factor for patients with UTUC [11–14]. Lymphatics serve as a major pathway for metastatic spread in many types of cancers. A number of studies show that when strictly evaluated, the addition of LVI to the standard pathological protocol improves its accuracy in the prediction of cancer specific survival and disease recurrence for patients with UTUC, especially for node-negative UTUC [11, 15, 16]. Some researchers have even proposed its inclusion as part of the TNM staging system, similar to hepatic and testicular cancer. Limitation to this is the difficulty in determining its presence on a morphological level with differences between pathologists [17]. Previous reports show that HE staining might be enough to asses routinely for any vascular invasion [18]. In our study assessment of LVI which was made on HE stained sections, the LVI rate was found to be 46.6%. From patients reported to be positive with LVI, 9.6% were alive at time of follow-up while from the patients negative for LVI, 75% were alive. A negative relationship was found between LVI and OS (p <0.001). LVI was also associated with the male gender, high grading and tumor necrosis (p = 0.017; <0.001 and <0.001 respectively). On the multivariate analysis LVI remained the only variable with a statistical significance (p value <0.001, HR = 11.089), which corresponds to the literature [19]. Risk stratification based on the LVI status would be helpful for selecting patients at high risk who would be appropriate candidates for clinical trials studying the effects of adjuvant chemotherapy in N_0M_0 disease [13].

Tumor necrosis was addressed as a prognostic criterion in a small number of reports. Langner et al. showed its significance as an independent predictive factor for OS and could predict distant metastasis after RNU [20]. This was confirmed by Simone et al. and other large series [10, 21, 22]. On a multivariate analysis tumor necrosis was an independent factor for cancer specific survival suggested to become part of pathological reporting [22]. In our study, tumor necrosis was found in 23.3% of patients. OS rate among the patients with tumor necrosis was estimated to be 7.1% while for patients without tumor necrosis this percent was 56.5%. There was a statistically significant correlation between the tumor necrosis and OS (p <0.001).

The prognostic role of concomitant non-muscle invasive bladder cancer or previous history of such, in patient with UTUC is investigated in limited amount of studies. In their meta-analysis Seisen T et al.

analyzed the outcomes of concomitant bladder cancer in 4,805 patients, where it was detected in 29% of the cases. Milojevich et al. performed analysis of 221 patients treated surgically for UTUC. There was 28% of the patients who had previous history of bladder carcinoma not invading the bladder muscle. Both studies concluded that previous history of non-muscle invasive bladder cancer had no effect on non-bladder recurrences, cancer specific survival and OS on patients with UTUC. In our series the previous history of non-muscle invasive bladder cancer had no significant statistical significance as a prognostic factor for OS and CSS (p = 0.584). It was detected in 17 (28.33%) of the patients, which correlates with literature [26, 30].

Limited amount of studies are performed regarding tumor size in patients with UTUC [27, 28]. Investigating a series of 162 patients Simone et al. concluded that tumor diameter ≥3 cm on both uni- and multivariate analysis has serious prognostic effect regarding cancer specific survival and OS. In the same study, larger size was found to correlate strongly with high grade and tumor necrosis (p <0.001). Shimamoto et al. in a series of 105 patients also found tumor diameter ≥3 cm is an independent prognostic factor for intravesical recurrence, distant metastasis and cancer specific survival. In our series sufficient information for tumor size was found for 34 of the patients. Despite the relatively small number of patients, the statistical analysis of our series found significant association with OS (p = 0.018). No statistically significant associations were found between tumor size and other variables which is probably due to the small number of patients.

Despite the obtained data, our study has limitations which are its retrospective nature and the relatively small number of patients. Furthermore, the increasing drop-out rates observed during the follow-up, reaching up to 45%, were another limitation.

CONCLUSIONS

On the univariate analysis, variables such as gender, grading, tumor stage, LVI and tumor necrosis were all demonstrated to be significant prognostic factors affecting CSS and OS after RNU in a patient with UTUC. On the other hand on the multivariate analysis only LVI remained statistically significant. LVI may explain the different clinical course in patients independently and might be considered as part of the pathological reporting and treatment planning.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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