Independent Predictors of Cancer-specific Survival in Transitional Cell Carcinoma of the Upper Urinary Tract

Multi-institutional Dataset From 3 European Centers

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BACKGROUND. The objective of the current study was to identify variables that were predictive of cancer-specific survival in patients with nonmetastatic transitional cell carcinoma of the upper urinary tract (UUT-TCC).

METHODS. Clinical and pathologic data from 269 patients who underwent nephroureterectomy for UUT-TCC from 1989 to 2005 in 3 urologic European centers were collected retrospectively. Log-rank tests and Cox proportional-hazards regression models were used for univariate and multivariate analyses.

RESULTS. Two hundred fifty patients underwent nephroureterectomy, and 19 patients underwent concomitant cystectomy for synchronous muscle-invasive bladder cancer. The median follow-up of the whole cohort was 34 months, and the median follow-up of the patients who remained alive and disease-free was 52 months. At follow-up, 57 cancer-related deaths (21.2%) were censored, and 169 patients (62.8%) were alive and disease-free. On univariate analysis, a history of previous bladder cancer, pathologic stage of the primary tumor and lymph nodes, tumor grade, the presence of lymphovascular invasion, tumor site, synchronous muscle-invasive bladder TCC, and tumor multifocality were associated with cancer-specific survival probabilities. On multivariate analysis, pathologic stage of the primary tumor and lymph nodes, synchronous muscle-invasive bladder TCC, and tumor multifocality were independent predictors of cancer-specific survival probabilities.

CONCLUSIONS. In a multi-institutional dataset of patients who had undergone nephroureterectomy for UUT-TCC, the current results indicated that pathologic stage of the primary tumor and lymph nodes, a history of prior bladder TCC, the presence of synchronous muscle-invasive bladder cancer, and tumor multifocality within the UUT were independent predictors of cancer-specific survival probabilities.

KEYWORDS: upper urinary tract transitional cell carcinoma, nephroureterectomy, ureterectomy, bladder cancer, cancer-specific survival.

Transitional cell carcinoma (TCC) of the upper urinary tract (UUT-TCC) is quite an uncommon disease. Epidemiologic data are limited, because the figures for kidney and renal pelvis cancers are reported clustered together, without distinguishing renal cell carcinoma and TCC.1 It is estimated, however, that renal pelvic TCC accounts for approximately 10% of all renal tumors and for approximately 5% of all urothelial tumors.2 Considering ureteral TCC as well, those estimates suggest that >3000 patients may be diagnosed with UUT-TCC in the United States in 2007. Moreover, data from...
The knowledge of prognostic factors for UUT-TCC often is based on studies on the most common bladder TCC, and only a few studies on prognostic factors for UUT-TCC have been published to date, and those sometimes have reported conflicting data. Tumor stage\(^4\)--\(^11\) and histologic grade\(^7\),\(^11\),\(^12\) are among the best established prognostic factors; whereas, conversely, the roles of other potentially relevant variables, such as a history of bladder cancer, tumor site, lymphovascular invasion, or multifocality, are less clear.\(^6\)--\(^8\),\(^10\),\(^11\) A clear knowledge of those prognostic data would be useful for counseling patients after surgery and for identifying those patients with unfavorable cancer-related outcome who may be candidates for future neoadjuvant or adjuvant randomized controlled trials. The objective of the current study was to identify the independent prognostic factors that predict cancer-specific survival in a multi-institutional dataset of patients with UUT-TCC by collecting the experiences of 3 major European centers.

**MATERIALS AND METHODS**

We analyzed the clinical data from 269 patients who had undergone nephroureterectomy for nonmetastatic UUT-TCC from 1989 to 2005 in 3 European urologic centers: Padua and Verona in Italy and Rennes in France. Chest x-rays and abdominal computed tomography scans were obtained preoperatively in each patient. Bone scans were obtained in patients with symptoms.

Surgery was performed by several surgeons according to the standard criteria for radical nephroureterectomy, ie, transabdominal extravesical dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff.\(^4\) The hilar and regional lymph nodes adjacent to the ipsilateral great vessel routinely were resected along with enlarged lymph nodes that were detected on preoperative computed tomography scans or palpable lymph nodes that were identified by intraoperative examination. No patients received neoadjuvant or adjuvant chemotherapy, although chemotherapy often was used to treat patients who had disease progression, with schemes differing according to the centers and years.

The following clinicopathologic data were extracted from the databases of each center: age; sex; history of prior UUT-TCC; history of prior bladder TCC; presence of synchronous muscle-invasive bladder TCC; number and site of UUT-TCC lesion(s); pathologic tumor, lymph node, metastasis (TNM) classification; tumor grade; presence of lymphovascular invasion; and follow-up data. With regard to the pathologic disease stage, all neoplasms were classified according to the 2002 TNM staging system.\(^13\) Histologic grades were assigned according to the 3-tiered World Health Organization classification.\(^14\) Lymphovascular invasion was defined as the observation of tumor cells in the luminal space lined by endothelial cells in hematoxylin and eosin-stained sections.\(^9\)

Follow-up schedules differed slightly among the centers but included cystoscopy and urine cytology at 3- to 4-month intervals for the first 2 years, at 6-month intervals for the subsequent 3 years, and annually thereafter. Excretory urograms or contrast computed tomography scans were obtained annually during follow-up or when clinically indicated.

Data on survival were taken from the clinical files of each center and, when necessary, by contacting the patients’ general practitioners or relatives or by searching through death records. All procedures were conducted in accordance with the ethical standards established in our institutions. Internal review board approval is not required for retrospective analyses dealing with archived material obtained during routine medical treatment.

**Statistical Analysis**

Continuous normally distributed variables were reported as the mean value ± standard deviation. Continuous non-normal variables were presented as the median values and interquartile ranges. The survival intervals were defined as the time elapsed from surgery to the last clinical evaluation or the patient’s death. The survival curves were estimated using the Kaplan–Meier method. Patients who were alive or who had died of other causes were censored (disease-specific survival). The log-rank test was used for comparison of the survival curves and for the univariate analysis. For the multivariate analysis, we assessed the assumption of proportionality through the analysis of Schoenfeld residuals of the covariate introduced in the model. Because of the presence of several covariates for which the assumption of proportionality was not satisfied, we used the extension of the Cox proportional-hazards model for time-dependent variables to build the stepwise multivariate model.

For all statistical analyses, a 2-sided \(P\) value <.05 was considered statistically significant. All data were analyzed with the Statistical Package for Social


### RESULTS

One hundred forty-three patients (53.1%) were treated in Padua, 43 patients (16%) were treated in Rennes, and 83 patients (30.9%) were treated in Verona. Two hundred fifty patients underwent nephroureterectomy, whereas 19 patients underwent contemporary nephroureterectomy and cystectomy for synchronous muscle-invasive bladder cancer.

Table 1 summarizes the clinical and pathologic characteristics of the 269 patients analyzed. The median follow-up duration of the whole cohort was 34 months (interquartile range, 13–66 months). Considering only the patients who remained alive and disease-free, the median follow-up duration was 52 months (interquartile range, 19–80 months).

At follow-up, we censored 57 cancer-related deaths (21.2%) and 34 deaths from other causes (12.6%). One hundred sixty-nine patients (62.8%) remained alive and disease-free (Fig. 1). On univariate analysis, the following variables were associated with cancer-specific survival probabilities: history of previous bladder cancer (log-rank $P = .007$) (Fig. 2), synchronous muscle-invasive bladder TCC (log-rank $P < .0001$) (Fig. 3), pathologic stage of the primary tumor (pT) (log-rank $P < .0001$) (Fig. 4) and lymph nodes (log-rank $P < .0001$), tumor grade (log-rank $P = .0002$), presence of lymphatic and/or vascular invasion (log-rank $P = .0002$), surgical margin status (log-rank $P = .0013$), tumor site (log-rank $P = .0008$), and tumor multifocality ($P < .0001$).

### TABLE 1

Clinical and Pathologic Characteristics of the 269 Analyzed Patients

| Characteristic                                      | No. of patients (%) |
|----------------------------------------------------|---------------------|
| **Center**                                         |                     |
| Padua                                              | 143 (53.2)          |
| Rennes                                             | 43 (16)             |
| Verona                                             | 83 (30.9)           |
| **Sex**                                            |                     |
| Men                                                 | 199 (74)            |
| Women                                               | 70 (26)             |
| **Mean ± SD age at surgery, y**                     | 67.7 ± 9.3          |
| **Prior history of UUT-TCC**                        |                     |
| Absent                                             | 234 (87)            |
| Present                                            | 35 (13)             |
| **Site of the UUT-TCC**                             |                     |
| Renal pelvis                                        | 101 (37.5)          |
| Ureter                                              | 92 (34.2)           |
| Pelvis and ureter                                   | 76 (28.3)           |
| **Site of the UUT-TCC**                             |                     |
| Renal pelvis                                        | 101 (37.5)          |
| Ureter                                              | 92 (34.2)           |
| Pelvis and ureter                                   | 76 (28.3)           |
| **Pathologic stage of the primary tumor**           |                     |
| T0                                                  | 4 (1.5)             |
| Ta-T1                                               | 118 (43.9)          |
| T2                                                  | 55 (20.4)           |
| T3                                                  | 76 (28.3)           |
| T4                                                  | 16 (5.9)            |
| Associated carcinoma in situ                        | 239 (88.8)          |
| Present                                             | 30 (11.2)           |
| **Pathologic lymph node stage**                     | 242 (90)            |
| N+                                                 | 27 (10)             |
| **Histologic grade**                                |                     |
| 1                                                   | 2 (0.7)             |
| 2                                                   | 111 (41.3)          |
| 3                                                   | 134 (49.8)          |
| X                                                   | 22 (8.2)            |
| **Lymphovascular invasion**                         | 225 (83.6)          |
| Present                                             | 44 (16.4)           |

SD indicates standard deviation; UUT, upper urinary tract; TCC, transitional cell carcinoma.

Sciences software, version 14.0 (SPSS Inc., Chicago, Ill) by the first author.

**FIGURE 1.** Cancer-specific survival is illustrated for the 269 patients who underwent nephroureterectomy for transitional cell carcinoma of the upper urinary tract. The 5-year cancer-specific survival probability was 76.1%.
(Table 2). With regard to a prior history of bladder TCC, patients with de novo UUT-TCC and those with prior nonmuscle-invasive bladder TCC had similar cancer-specific survival probabilities (log-rank *P* = .057). The survival probabilities differed significantly between patients with nonmuscle-invasive bladder TCC and patients with muscle-invasive bladder TCC (log-rank *P* = .002).

With regard to the pathologic stage of the primary tumor, the patients with pT0-Ta-T1 cancers had disease-specific survival probabilities similar to those for patients with pT2 cancers (log-rank *P* = .052); in addition, the difference in the survival probability was statistically significantly between patients with pT2 tumors and pT3 tumors (log-rank *P* < .001) and between patients with pT3 tumors and pT4 tumors (log-rank *P* < .001) (Fig. 4). Statistically nonsignificant differences in the disease-specific survival probabilities also were observed between patients with grade 1 and 2 UUT-TCC (log-rank *P* = .75), patients with grade 3 and X TCC (log-rank *P* = .26), and patients with pelvic or ureteral TCC (log-rank *P* = .58). Consequently, those categories were clustered together to generate the multivariate model. Using the analysis of Schoenfeld residuals of the covariates introduced into the model, the assumption of proportionality was satisfied only for 2 covariates (pathologic lymph node stage and tumor multifocality). Consequently, the extension of the Cox proportional-hazards model for time-dependent variables was used to build the stepwise multivariate model, in which the following variables were independent predictors of cancer-specific survival probabilities: history of bladder TCC before the diagnosis of UUT-TCC (hazard ratio [HR], 1.743; *P* = .01), pathologic stage of the primary tumor (HR, 3.346; *P* < .001) and lymph nodes (HR, 2.978; *P* = .001), tumor multifocality within the UUT (HR, 2.971; *P* < .001), and presence of synchronous muscle-invasive bladder TCC (HR, 4.687; *P* < .001) (Table 3).

**DISCUSSION**

To our knowledge, the current study is one of the largest published series of nephroureterectomy for UUT-TCC to assess the prognostic value of several clinical and pathologic variables for cancer-specific survival. Our analysis indicated the independent predictive role of the pathologic stage of both the
primary tumor and the lymph nodes, as well as a prior history of bladder TCC, the presence of synchronous muscle-invasive bladder TCC, and tumor multifocality in the UUT; whereas other pathologic variables, such as histologic grade and the presence of lymphovascular invasion, failed to reach statistical significance.

Pathologic stages of the primary tumor and lymph nodes probably are the best established pathologic predictors of cancer-specific survival. Guinan et al., who reported the largest published series of >600 patients who were treated in Illinois, observed that the 5-year cancer-specific survival probabilities were 75% for patients with Ta/tumor in situ (Tis) tumors, 87% for patients with T1 and T2 tumors, 54% for patients with T3 tumors, and 19% for T4 patients. More recently, Hall et al. reported 5-year cancer-specific survival probabilities of 100% for patients with Ta/Tis tumors, 92% for patients with T1 tumors, 73% for patients with T2 tumors, and 41% for patients with T3 tumors.

With regard to histologic grade, data from the literature indicate 5-year cancer-specific survival probabilities in the range from 80% to 100% for patients with grade 1 UUT-TCC, from 33% to 94% for patients with grade 2 UUT-TCC, and from 11% to 40% for patients with grade 3 UUT-TCC. Moreover, a few studies reported the independent prognostic role of grade, indicating that patients who have high-grade cancers have at least 2-fold increased risk of cancer-related death compared with patients.
who have low-grade cancers.\textsuperscript{18} Our analysis failed to prove the independent prognostic role of histologic grade, which also happened in other large series.\textsuperscript{4,8–10} This may have been caused by the lack of a significant difference in survival between patients with grade 1 tumors and grade 2 tumors and by the lack of significant reproducibility in the diagnosis of grade in TCC.

A major issue in UUT-TCC is the prognostic role of a history of bladder cancer. In our series, a history of bladder TCC was identified in approximately 50% of patients, and 7% of those patients harbored synchronous muscle-invasive bladder cancers that required concomitant cystectomy. Those proportions were far greater than what was reported previously in the literature, in which bladder TCC reportedly was present in from 9% to 20% of patients who underwent nephroureterectomy.\textsuperscript{4,11,19} In our analysis, the presence of bladder cancer before the diagnosis of UUT-TCC turned out to be an independent predictor of the probability of cancer-specific survival, but this was because of the small number of patients with muscle-invasive bladder cancer, who underwent radical cystectomy before nephroureterectomy.\textsuperscript{4,11,19} In our analyses, nonmuscle-invasive bladder TCC did not play a major prognostic role, and the small difference in the 5-year cancer-specific survival probabilities between patients without prior bladder cancer and patients with nonmuscle-invasive bladder cancer showed only a statistically nonsignificant trend. Conversely, Mullerad et al., in their series of 129 patients from the Memorial Sloan-Kettering Cancer Center, reported that a history of bladder TCC was an independent predictor of cancer-specific survival in multivariate analysis, with a history of bladder TCC having an adverse effect on patient prognosis.\textsuperscript{8} However, Rabbani et al. reported data from the SEER database comparing tumor characteristics and outcomes for 657 patients who had UTT-TCC diagnosed after bladder cancer with those of 7839 patients who had de novo UTT-TCC. In their multivariate analysis, de novo UTT-TCC had a 1.67-fold increased risk of cancer-related death compared with secondary TCC.\textsuperscript{7} Further data are available on the role of bladder TCC concomitant to the UUT-TCC. Kang et al. reported on a large series of patients with UUT cancers who were treated mostly by nephroureterectomy in Taiwan.\textsuperscript{18} Those authors demonstrated that the presence of concomitant bladder cancer at the moment of the treatment for UUT-TCC was an independent predictor of cancer-specific survival, along with stage, grade, and preoperative renal function.\textsuperscript{18} Those data were similar to ours, because we demonstrated that synchronous muscle-invasive bladder cancer significantly impaired patients’ survival.

Within the UUT, patients who have cancers arising from the renal pelvis reportedly have a better cancer-related outcome than patients who have cancers in the ureter; and a few studies have indicated that tumor site was an independent predictor of cancer-specific survival.\textsuperscript{11,20} Conversely, van der Poel et al. demonstrated that patients who had tumors in the renal pelvis and proximal ureter were 2.5 times more likely to die of disease compared with patients who had tumors in the distal ureter, reconfirming the data even in multivariate analyses.\textsuperscript{10} In our series, patients with pelvic or ureteral cancers had similar survival probabilities, which were higher than those for the patients who harbored concomitant pelvic and ureteral cancers, although the data were not significant on multivariate analysis. This may be explained in part because we reported only on patients who underwent nephroureterectomy, whereas patients with only ureteral TCC who underwent ureterectomy and reimplantation were not included in the current analysis.

In our series, tumor multifocality within the UUT was an independent predictor of cancer-specific

| TABLE 3 |
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| Multivariate Analysis of Prognostic Factors for 5-Year Cancer-specific Survival: Cox Proportional-hazards Model |
| Variable | Reference level | HR | 95% CI | \( P \) |
| Prior history of bladder TCC | Absent or nonmuscle-invasive vs muscle-invasive TCC | 1.743 | 1.140–2.665 | .010 |
| Muscle-invasive bladder TCC at nephroureterectomy | Absent vs present | 4.687 | 2.326–9.443 | <.001 |
| Multifocality | Absent vs present | 2.971 | 1.356–6.429 | <.001 |
| Pathologic stage of primary tumor | \(<pT2 vs pT3 vs pT4\) | 3.346 | 2.231–5.018 | <.001 |
| Pathologic lymph node stage | N0 vs N+ | 2.978 | 1.323–5.824 | .001 |

HR indicates hazard ratio; 95% CI, 95% confidence interval; TCC, transitional cell carcinoma; \( pT \), pathologic tumor stage; N, lymph node stage.
survival. These data were quite original in the literature, because other reports on this issue failed to demonstrate a significant prognostic role in multivariate analysis. These features, along with the prognostic role of prior or concomitant bladder cancers, strongly reconfirm the panurothelial nature of the disease.

It has been demonstrated that the presence of lymphovascular invasion is an important prognostic factor in other urologic malignancies, including prostate cancer, squamous cell carcinoma of the penis, and bladder TCC. Hong et al., reporting on a series of 86 patients who underwent nephroureterectomy for UUT-TCC, demonstrated that lymphovascular invasion was an independent prognostic factor for recurrence-free (but not cancer-specific) survival probabilities. In our series, however, lymphovascular invasion was predictive of neither cancer-specific nor progression-free survival (data not shown).

Table 4 summarizes the role of the prognostic factors of cancer-specific survival in the main published articles showing formal multivariate models (Table 4). These data on patients’ prognoses are useful for several reasons. First, these data, either individually or within prognostic nomograms, can be useful for counseling patients after surgery. Second, a clear knowledge of prognostic factors enables us to identify patients with unfavorable cancer-related outcomes who may be candidates for future neoadjuvant or, rather, adjuvant randomized controlled trials or further studies on molecular markers.

Our study had several drawbacks. The data were collected retrospectively, which prevented us from assessing several potentially important variables, such as the presence of symptoms, patients’ performance status or comorbidity, molecular markers, the role of systemic therapies, and so on. Moreover, our pathologic data were obtained from the surgical pathology reports in patients’ clinical records without revisions of the slides by central or local pathologists. Moreover, although it was large, our series may not have been powered sufficiently to detect small differences in survival among the different categories of patients or to test all pairwise interactions between the variables in the multivariate model. Moreover, our study did not include patients who underwent distal ureterectomy and ureteral reimplantation for ureteral TCC.

In conclusion, in our multi-institutional dataset of patients who underwent nephroureterectomy for UUT-TCC, we demonstrated that the pathologic stage of the primary tumor and lymph nodes, a history of bladder TCC before the diagnosis of UUT-TCC, tumor multifocality within the UUT, and synchronous muscle-invasive bladder cancer were independent predictors of cancer-specific survival probabilities. These factors may be useful for counseling patients after surgery and for identifying patients with unfavorable cancer-related outcomes who may be candidates for future neoadjuvant or adjuvant randomized controlled trials.

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