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ABILITY OF CLINICAL GRADE TO PREDICT FINAL PATHOLOGIC STAGE IN UPPER URINARY TRACT TRANSITIONAL CELL CARCINOMA: IMPLICATIONS FOR THERAPY

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Abstract

Objective: To evaluate whether clinical grade predicts final pathologic stage in upper urinary tract transitional cell carcinoma (UTTCC).

Methods: We retrospectively reviewed the records of 184 consecutive patients undergoing nephroureterectomy for UTTCC at our institution between 1986 and 2004. Their clinical, surgical, and pathological data were reviewed to determine the positive and negative predictive values (PPV and NPV) of clinical biopsy grade with respect to final pathologic stage of disease.

Results: In all, 119 (64.7%) patients had information available regarding the clinical grade of disease from preoperative endoscopic biopsy. The distribution of clinical grades was grade 1: 2 (1.6%), grade 2: 46 (38.7%) and grade 3 in 71 (59.7%) patients. Of the 71 patients with grade 3 disease 47 had $\geq$ pT2 disease (66% PPV). Of the 48 patients with less than grade 3 disease 35 had $<$ pT2 disease (72% NPV). Of the 71 patients with grade 3 disease 30 had $\geq$ pT3 disease (42% PPV). Of the 48 patients with less than grade 3 disease, 44 had $<$ pT3 disease (92% NPV).

Conclusion: Histologic grade obtained on diagnostic biopsy for UTTCC may be used to predict pathologic stage of disease. This information can be used to counsel patients before surgery and to identify patients for whom neoadjuvant chemotherapy would be most beneficial.

Keywords

renal pelvis; ureter; transitional cell carcinoma; grade; stage; survival

INTRODUCTION

Transitional cell carcinoma of the upper urinary tract (UTTCC) accounts for 5% to 7% of all urothelial malignancies.¹ The definitive surgical treatment for this disease remains

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nephroureterectomy conducted through either open or a laparoscopic approach. In patients undergoing nephroureterectomy, the impact of pathologic tumor grade, stage, and lymph node status on patient survival is well documented.^{2,3} The 5-year disease-specific survival (DSS) rate for patients with pT1 tumors is reported to be 91.7%, and survival decreases significantly with increasing stage, such that patients with pT4 tumors have a median DSS of only 6 months.² Unfortunately, the outcomes for patients with invasive ($\geq$ pT2) disease have not changed significantly over the past two decades, suggesting that a change in therapeutic approach is required.

Prior studies have indicated that neoadjuvant chemotherapy can improve survival in patients with high-risk bladder cancer, and a small study⁴ showed that neoadjuvant chemotherapy improved survival in patients with invasive UTTCC. Successful use of neoadjuvant chemotherapy in patients with UTTCC would require the ability to predict, pre-operatively, which patients have pT2 or higher disease since these patients are most likely to benefit from multimodal therapy.^{2,3} We evaluated, in a single-institutional series of 184 patients with primary UTTCC, whether grade on preoperative diagnostic biopsy can be used to predict pathologic stage.

MATERIALS AND METHODS

After obtaining institutional review board approval, we searched our surgical and tumor database to identify patients with transitional cell carcinoma of the renal pelvis and ureter who underwent nephroureterectomy with curative intent at our institution between 1986 and 2004. From these patients, we selected those who had undergone tissue biopsy at the time of ureteroscopy. To limit variations in pathologic specimen interpretation and to eliminate concerns regarding tumor understaging, we excluded patients treated with endoscopy alone, those with nontransitional disease, those with surgically unresectable disease, and those who underwent surgery elsewhere.

Pretreatment evaluation included a complete medical history, physical examination, and laboratory evaluation. Cystoscopy, retrograde pyelography, and ureteroscopy were performed on all patients to confirm the diagnosis of UTTCC. At the time of diagnosis, all pathology specimens were reviewed by a genitourinary pathologist and graded according to the World Health Organization grading system and staged according to the^{5,6} tumor-node-metastasis classification system of the International Union Against Cancer. Tumor grade was assigned according to the World Health Organization classification of urothelial carcinomas. Nephroureterectomy was performed via an open technique using a subcostal, midline, or flank incision with bladder-cuff excision. In recent years, laparoscopic radical nephroureterectomy was performed using hand-assisted or conventional methods with open bladder-cuff excision and intact specimen extraction.

The pathology records were reviewed, and the preoperative clinical tumor grade was collected. For purpose of analysis, patients were classified into one of two categories on the basis of their preoperative diagnostic biopsy grade: low- or intermediate-grade disease (grade 1 and grade 2) and high-grade disease (grade 3). Patients with carcinoma in situ alone on preoperative diagnostic biopsy were excluded from this analysis (n=3).

STATISTICAL ANALYSIS

The ability of preoperative clinical grade to predict pathologic disease stage was evaluated by determining the positive and negative predictive values (PPV and NPV) of preoperative biopsy grade with respect to pathologic stage. Two PPVs were calculated: the probability of having pT2 or higher disease and the probability of having pT3 or higher disease if the clinical grade was 3. Two NPVs were calculated: the probability of having less than pT2 disease and the

probability of having less than pT3 disease if the clinical grade was less than 3. Additionally, exact 95% confidence intervals (CIs) were calculated to estimate the PPVs and NPVs. For patients with multifocal disease, the worst clinical grade of disease was used for calculating the PPVs and NPVs.

Survival times were calculated in the number of years from the date of nephroureterectomy. Overall survival and DSS were estimated utilizing the methods of Kaplan and Meier. Cox's proportional hazards regression model was used to test the statistical significance of several potential prognostic factors for overall survival, DSS, and recurrence-free survival. This model was done in univariate fashion. All prognostic factors with a significance value of $P < 0.25$ from the univariate analysis were then included in a saturated model, and backward elimination was used to remove factors from the model on the basis of likelihood ratios in multiple regression analysis. StatXact, version 4.0.1, (Cytel, Inc., Cambridge, MA) was utilized for all statistical analyses.

RESULTS

Our retrospective review identified 184 patients treated with nephroureterectomy for UTTCC during the study period. One hundred nineteen of these (64.7%) underwent tissue biopsy at the time of ureteroscopy and had data available on preoperative clinical grade. As seen in Table I, there was a predominance of grade 3 tumors (59.7%) on preoperative diagnostic biopsy. Final pathologic analysis confirmed grade 3 tumors in 62.3% of patients. Seven patients (5.9%) had a discrepancy between the preoperative clinical and final pathologic grades. On final pathologic analysis, 50.4% of the patients had at least muscle-invasive tumors (pT2 or higher disease). The median duration of follow-up was 2.5 years (range 0.1 to 17.9) for all patients, 2.7 years (range 0.1 to 17.9) for patients alive at the time of this analysis, and 2.1 years (range 0.3 to 12.8) for patients who had died.

SURVIVAL ANALYSES

Kaplan-Meier analysis of all 184 patients undergoing nephroureterectomy for UTTCC was performed to identify the impact of tumor stage and grade on survival. The median DSS was 12.8 years. In patients with solitary tumors, the location of disease was not a significant factor in patient survival ($p=0.17$). If we looked at biopsy grade, patients with clinical grade 3 disease had a markedly lower DSS survival rate at 10 years than patients with grade 1 or 2 disease had: 46.2% versus 85.6% (Figure 1a.). Patients with less than pT2 disease had a 10-year DSS rate of 89.7%, whereas those with $\geq$ pT2 or $\geq$ pT3 disease had 10-year DSS rates of 41.3% and 27.5% respectively (Figure 1b).

RELATIONSHIP BETWEEN CLINICAL GRADE AND PATHOLOGIC STAGE

Table II shows the relationship between preoperative clinical grade and final pathologic stage of disease. Of the 71 patients with clinical grade 3 disease, 47 (66.2% PPV) had pT2 or higher disease (95% confidence interval [CI]: 54.0% to 77.0%), and 30 (42.3% PPV) had pT3 or higher disease (95% CI: 30.6% to 54.6%). Of the 48 patients with less than clinical grade 3 disease, 35 (72.9% NPV) had less than pT2 disease (95% CI: 68.2% to 84.7%), and 44 (91.7% NPV) had less than pT3 disease (95% CI: 80.0% to 97.7%). Thus, patients with clinical grade 3 tumors had a 66.2% chance of having pT2 or higher disease and a 42.3% chance of having pT3 or higher disease. Conversely, patients with clinical grade 1 or 2 tumors had only a 28.3% chance of having pT2 or higher disease and only a 8.7% chance of having pT3 or higher disease.

COMMENT

Our analysis demonstrates that patients with grade 3 UTTCC on preoperative diagnostic biopsy have a substantial likelihood of harboring invasive UTTCC. Conversely those with grade 1 or 2 UTTCC have a minimal risk of invasive disease.

For bladder cancer, combining neoadjuvant chemotherapy with surgery has led to improved results in selected patients.⁷ This approach has the potential to downstage tumors and treat micrometastatic disease in the setting of maximal renal reserve. Grossman *et al.* recently reported a survival benefit (77 vs 46 months; $p=0.06$) in patients with $\geq pT2$ bladder cancer who received neoadjuvant chemotherapy followed by cystectomy compared to those treated with cystectomy alone.⁷ Additionally, these authors observed that receiving preoperative chemotherapy did not prevent patients from undergoing surgery or increase surgery-related complications.^{7,8}

Results of a recent small series suggest that a neoadjuvant-chemotherapy treatment paradigm similar to the one currently utilized in urothelial carcinoma of the bladder may be applicable to UTTCC. Igawa *et al.* reported that in a series of 15 patients with locally advanced UTTCC treated with neoadjuvant cisplatin-based chemotherapy followed by nephroureterectomy, the overall response rate was 54%, and two patients had their tumors downstaged to pT0.⁴ Although the number of patients in the series was small, a survival advantage was observed in the patients with pT0 disease compared to the remaining patients.⁴ Further evidence in support of neoadjuvant chemotherapy for UTTCC comes from our own present series. In our series, the 10-year DSS rate in patients with invasive (pT2 or higher) disease was 65%, whereas the corresponding rate in patients with noninvasive (less than pT2) disease was 87%. This would suggest that surgical therapy alone, as it is currently utilized, is not adequate therapy for patients with invasive UTTCC.

Application of the neoadjuvant-chemotherapy approach to UTTCC would require a preoperative assessment of risk, to determine which tumors are likely to result in reduced patient DSS and thus which patients are the best candidates for neoadjuvant chemotherapy. Some method of risk stratification is required such that patients who would benefit may receive neoadjuvant chemotherapy in the presence of maximal renal function and those who would not benefit can avoid overtreatment. The findings of our study indicate that using tumor grade on preoperative diagnostic biopsy as a predictor of final pathologic stage of disease will allow us to risk-stratify patients and offer neoadjuvant therapy to those who may derive maximal benefit while reducing concerns about overtreatment. Specifically, our findings indicate that if we use pT2 or higher disease as the threshold for offering neoadjuvant chemotherapy, the presence of clinical grade 3 disease on preoperative biopsy would correctly identify over 66% of the patients who should be offered this therapy. Conversely, the presence of clinical grade 1 or 2 disease on preoperative biopsy would correctly identify over 71% of the patients who should not be offered this therapy. Our findings are in agreement with a prior report by Keeley *et al.*, who found correlation between the clinical grade of disease obtained on ureteroscopic biopsy and cytology and the final pathologic grade and stage of disease in UTTCC.⁹ In that study of 51 patients undergoing ureteroscopic biopsy prior to open surgical management of UTTCC, they reported that 66.7% of patients with clinical grade 3 disease had invasive (pT2 or pT3) tumors in the final pathologic specimen. Their report included not only information from biopsy but also cytology (more observer dependent) to biopsy grade. On the basis of our findings, the presence of grade 3 disease on preoperative biopsy is currently an inclusion criterion for the trials ongoing at our institution of neoadjuvant chemotherapy for UTTCC.

We acknowledge the limitations of this retrospective analysis of a surgical series. It is possible that since our patients all underwent nephroureterectomy, those with clinical grade 1 and 2

tumors might have had other clinical indicators suggesting more advanced stage. However, this would bias our results towards overestimation of invasive disease in such patients, and even so, we found that the NPV of grade 1 and 2 disease with respect to pT2 or higher disease was 71%. We also acknowledge that other factors could affect the predictive value of clinical grade with respect to pathologic stage, such as time to surgery, prior treatments, expertise of the pathologist, and imaging data. However, analyzing the effects of these factors within this single-center experience would result in comparisons of very small numbers of patients in each subset, leading to inherent inaccuracies of statistical analysis. We hope that our report will be validated in subsequent multi-institutional pooled analyses, and we hope that with larger numbers of patients, a nomogram to predict postoperative stage can be constructed.

CONCLUSIONS

Histologic grade obtained on diagnostic biopsy for UTTCC may be used to predict pathologic stage of disease. This information can be used to counsel patients before surgery and to identify patients for whom neoadjuvant chemotherapy would be most beneficial.

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Figure 1.

(A) Kaplan-Meier estimates of disease-specific survival by clinical grade.

(B) Kaplan-Meier estimates of disease-specific survival by pathologic stage.

Table 1
Demographic, clinical, and pathologic tumor characteristics of the study cohort

Characteristic	No. (%)
Age, median years (range)	67.3 (50-78) years
Sex (n = 184)	
Men	121 (65.7)
Women	63 (34.3)
Tumor location (n = 184)	
Renal pelvis	66 (35.9)
Ureter	57 (30.9)
Renal pelvis and ureter	61 (33.2)
Clinical tumor grade (n = 119)	
1	2 (1.6)
2	46 (38.7)
3	71 (59.7)
Pathologic stage (n = 119)	
Ta	26 (21.9)
Tis	7 (5.8)
T1	26 (21.9)
T2	26 (21.9)
T3	30 (25.2)
T4	4 (3.3)
Pathologic tumor grade (n = 119)	
1	2 (1.6)
2	43 (36.1)
3	74 (62.3)

Table 2

Relationship between clinical grade and pathologic stage of disease in 119 patients undergoing nephroureterectomy for UTTCC

Clinical Grade	Pathologic Stage, No. (%)			
	<pT2	≥pT2	<pT3	≥pT3
1	2/2 (100)	0/2 (0)	2/2 (100)	0/2 (0)
2	33/46 (71.7)	13/46 (28.3)	42/46 (91.3)	4/46 (8.7)
3	24/71 (33.8)	47/71 (66.2)	41/71 (57.7)	30/71 (42.3)