



11-2014

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Recommended Citation

Amirian, Michael J.; Radadia, Kushan; Narins, Hadley; Healy, Kelly A.; Hubosky, Scott G.; Bagley, Demetrius H.; Trabulsi, Edouard J.; and Lallas, Costas D., "The significance of functional renal obstruction in predicting pathologic stage of upper tract urothelial carcinoma." (2014). *Department of Urology Faculty Papers*. Paper 31.

<http://jdc.jefferson.edu/urologyfp/31>

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**The Significance of Functional Renal Obstruction in
Predicting Pathologic Stage of Upper Tract Urothelial Carcinoma**

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Key Words: advanced urothelial carcinoma; upper tract; renal obstruction

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Abstract

INTRODUCTION AND OBJECTIVES: Assessing the severity of upper tract urothelial carcinoma (UTUC) has been difficult because of inadequate biopsy specimens. Additional predictive parameters of disease stage would be useful when deciding a treatment plan; it has been suggested that preoperative hydronephrosis can be a surrogate. We examined the relationship between preoperative ipsilateral renal obstruction identified by imaging with final pathologic stage after nephroureterectomy (NU) for UTUC. We then analyzed those patients with ipsilateral renal obstruction and examined if tumor location is associated with an advanced pathologic stage.

METHODS: Patients who underwent NU for UTUC between the years 2001 to 2013 were analyzed and relevant staging studies and pathology were reviewed. Criteria for ipsilateral renal obstruction were defined by the presence of a delayed nephrogram on CT scan, renal cortical atrophy with associated hydronephrosis on cross-sectional imaging, and/or >10% split function discrepancy on nuclear renal scintigraphy with associated hydronephrosis.

RESULTS: Eighty-two patients met inclusion criteria; 26/82 (31.7%) had locally advanced disease (pT3/T4), while 56/82 (63.4%) had organ-confined (\leq pT2) disease. Of the patients with pT3/T4 disease, 10/26 (38.5%) demonstrated radiographic evidence of functional obstruction of the ipsilateral renal unit; similarly, in patients with \leq pT2 disease, 21/56 (37.5%) demonstrated ipsilateral renal obstruction ($p=0.93$). Of the patients with ipsilateral renal obstruction, in those patients with pT3/T4 disease, 7/10 (70.0%) had ureteral tumor involvement while 9/21 (42.9%) patients with \leq pT2 disease had tumor in the ureter ($p=0.25$).

CONCLUSIONS: This study suggests that renal obstruction by radiographic analysis does not always predict advanced stage. Additionally, there is a trend toward advanced stage when a patient has radiographic evidence of ipsilateral renal dysfunction and a ureteral tumor.

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare entity with respect to other genitourinary (GU) malignancies. It is reported that it accounts for approximately 5% of renal and urothelial tumors.^[1] In comparison to other GU malignancies, according to the American Cancer Society statistics for the United States in 2014, there will be approximately 6500-7000 new cases of UTUC in comparison to 233,000 prostate, 75,000 bladder, and 8800 testis cancer patients.^[2]

The gold standard for the treatment of UTUC is radical nephroureterectomy (NU) with bladder cuff excision. However in those patients who are surgically unfit, have a solitary kidney, bilateral UTUC, or chronic kidney disease, endoscopic management may be an alternative to preserve as much functioning nephron as possible; additionally, endoscopic management has been used electively in patients with low grade, focal UTUC and a normal contralateral kidney. It has also been shown that disease specific survival has a poorer outcome in those with chronic kidney disease.^[3]

Given that architectural preservation cannot be achieved with sampling of upper tract tumors, diagnosis and staging currently employ a multimodal approach of the following: ureteroscopy with direct visualization and biopsy, abdominal imaging via computed tomography (CT) or magnetic resonance imaging (MRI) to identify direct tumor extension, and endoluminal ultrasound, where available, which also may help to identify transmural involvement. Unfortunately, each modality has variable accuracy in predicting grade and stage and currently most treatment decisions are based upon ureteroscopy and specimen retrieval for cytopathological analysis and three-dimensional imaging.^[4-11]

Recently, the presence of hydronephrosis associated with or without renal obstruction on preoperative imaging was associated with worse prognosis and advanced stage UTUC on NU.^[13,14] Additionally, delayed ipsilateral renal excretion in patients with ureteral tumors has been associated with decreased survival on univariate analysis.^[15] We sought to confirm this relationship with our own, single-institutional UTUC population. Additionally, realizing that UTUC may have a different prognosis dependent on tumor location, we sought to determine if the location of the primary tumor (renal pelvis/calices versus ureter) changed this association.

Materials and Methods

After obtaining IRB approval, a retrospective analysis of consecutive patients undergoing NU at our institution between 2001 and 2013 was performed.

Each patient's preoperative staging studies, which included three-dimensional imaging and preoperative ureteroscopic biopsies and specimen cytology, were examined. Some patients in whom a NU was planned also obtained a scintigraphic renal scan in order to determine differential renal function and the ability of a remaining renal unit to sustain adequate function. A subset of patients in whom UTUC was being managed initially with serial endoscopic evaluations was evaluated using the highest histologic grade of tumor that was recovered endoscopically. Following surgery, the tissue specimens were examined for pathologic grade and stage in a multidisciplinary genitourinary pathology conference. Each patient's preoperative radiographic images were reviewed. Functional renal obstruction on preoperative imaging was defined by one of 3 variables:

1. Radiologic demonstration of delayed nephrogram unilaterally on CT scan as described by the radiologist;
2. The interpretation of ipsilateral renal cortical thinning with hydronephrosis in comparison to the contralateral kidney as described by the radiologist; and/or
3. >10% split function discrepancy on nuclear renal scan with associated hydronephrosis.

Summary statistics (n and percent) were calculated for the sample pre-NU stage, NU, Ipsilaterality, pathology stage, node status, symmetry, and change in staging. The relationship between pre-operative URS path grade and NU tumor stage was investigated in a few ways. Concordance was calculated between the two measures and agreement was assessed using the Kappa statistic. Predictive power of the pre-op URS path stage on NU tumor stage was assessed using the Receiver Operating Characteristic under the curve (ROC AUC) from a logistic regression model. A contingency table of ipsilateral decrease in renal function versus pathologic stage of UTUC was constructed and a Pearson's Chi-squared test used to assess the relationship of the two.

Results

We identified 82 patients who underwent NU. Seventy-five patients had a laparoscopic radical NU procedure, 7 had an open radical NU, and 3 patients attempted laparoscopically were converted to open. The mean age of the patient cohort was 69.2 +/- 11.2 years (33-95), as shown in Table 1. Laterality was evenly distributed: 41 right side moieties and 42 left side with 1 patient having a bilateral nephroureterectomy. The mean creatinine at the time of surgery was 1.4 +/- 0.95 mg/dL (0.6-6.9).

On final pathology, 37 patients had low grade UTUC, defined as grade 1, grade 1-2, or grade 2. Forty-one patients had high grade disease, defined as grade 2-3, or grade 3. Four patients did not have pathologic grade available (Table 2). For these, 2004 world health organization/International Society of Urological Pathology WHO/ISUP classification of tumors of urinary tract were used.

One patient did not have preoperative ureteroscopic biopsy grade information. The ureteroscopic biopsy grade correlated with final pathologic grade for the majority of patients. When comparing preoperative ureteroscopic biopsy grade to final pathologic grade, 54/81 (67%) of patients had identical tumor grade correlation between ureteroscopic and NU pathology. In 18/81 patients (22%), the tumor grade was upgraded from low grade to high grade on final surgical pathology, and 9/81 (11%) of patients were downgraded from high ureteroscopic biopsy grade to low grade on final surgical pathology (Table 2).

Final pathologic stage information is shown in Table 3. Four patients had no evidence of disease (pT0), 29 patients had organ confined disease (pT1/T2), and 26 patients had locally advanced disease (pT3/T4). The ability of ureteroscopic grade to predict final pathologic stage was next examined. Positive prediction was concluded if there was high grade ureteroscopic cytology and advanced pathologic stage (\geq pT3), or low grade ureteroscopic cytology and organ confined disease ($<$ pT3). Stage correlation overall was 42/73 (57.5%) of patients. Low grade ureteroscopic grade and pT2 or less disease correlated to 30/47 (63.8%) of patients. High grade ureteroscopic grade and pT3 or greater stage showed a 12/26 (46.1%) correlation. Nine patients were omitted from this calculation because of the lack of preoperative ureteroscopic grade or if the patient had carcinoma in situ, CIS (5 patients) as the only pathologic diagnosis (Table 3).

By utilizing our criteria for functional renal obstruction, we next analyzed our hypothesis. In total, 10 patients showed ipsilateral functional renal obstruction and \geq pT3 stage disease, while

16 patients had no renal obstruction and \geq pT3 stage disease. Contrarily, 21 patients had an ipsilateral renal obstruction with organ confined ($<$ pT3) stage, while 35 patients had no obstruction and $<$ pT3 disease. Thus 38.46% (10/26) patients with pT3 or greater disease showed ipsilateral renal obstruction in comparison to 37.50% (21/35) patients showing ipsilateral renal obstruction and organ confined disease ($p=0.9334$) as shown in Table 4. Of the patients with obstruction and \leq pT2 disease, 8 had delayed nephrogram on three-dimensional imaging, 4 had hydronephrosis with cortical thinning, and 11 had decreased differential function and hydronephrosis (2 patients met 2 separate criteria). For those with $>$ pT3 UTUC, none had delayed nephrogram, 3 had hydronephrosis with cortical thinning, and 7 had decreased differential function and hydronephrosis.

Of the patients with functional renal obstruction, patients staged at pT3 or greater, 7/10 (70.0%) patients had ureteral involvement (Table 5). When compared to those patients with functional renal obstruction and staged at \leq pT2, 9/21 (42.9%) patients had ureteral involvement ($p=0.252$).

Discussion

For UTUC, accurate clinical staging is vital to determine the proper course of surgical management, especially if endoscopic management, which is now considered appropriate for some patients who possess low grade disease and a normal contralateral kidney, is contemplated [16,17]. Currently, staging is limited to visual inspection via ureteroscopy with endoscopic biopsy and urine aspiration for cytopathological analysis. [4] Keely *et al.* reported on grade correlation between ureteroscopic biopsies and final NU specimens. Of those patients, 7/8 (88%) with low ureteroscopic biopsy grade were confirmed to have low grade disease on final surgical pathology. Additionally, for patients with high grade ureteroscopic biopsies, 11/12 (91.7%) had high grade tumors on final surgical pathology. In examining final pathologic stage, only 3/29 (10%) of patients with low grade ureteroscopic biopsy had muscle invasive disease (pT2 or greater), while 8/12 (67%) of high grade tumors were muscle invasive. [5] In comparison, our data showed that ureteroscopic biopsy was not completely reliable, correlating with final surgical pathology in 42/73 (57.5%) patients; low grade and \leq pT2 stage correlation was 30/47(63.8%), and high grade to \geq pT3 stage correlation was 12/26 (46.1%). It should be noted that the Keeley

series was also from this institution, although predating the current series by at least 10 years, and involving only one, as opposed to multiple, pathologists.

Recent data from Brown *et al.* noted that a high grade endoscopic biopsy corresponded to locally advanced disease on final surgical pathology in only 30/71 (42%) of patients.^[12] This uncertainty further demonstrates the need for more accurate diagnostic measures to predict final pathologic stage on initial radiographic and endoscopic evaluation. Additionally, prediction of stage by retrograde pyelogram was shown to be poor in a study by Keeley *et al.*, indicating only a 27% correlation between retrograde radiographic appearance and advanced disease.^[10] Finally, comparison of the visual appearance alone of a UTUC tumor with histologic grade has also been shown to be unreliable. El-Hakim *et al.* found that 30% of 40 patients were inaccurately classified based on appearance alone.^[6]

Abdominal imaging also has controversial ability to accurately determine pathologic stage of UTUC. Attempts to detect direct transmural tumor extension on multi-detector abdominal/pelvic CT (MDCT) scans, by examining ureteral wall thickness, loss of renal sinus fat, or abnormal adjacent fat parenchyma are unreliable in clinical practice. In a study conducted by Fritz *et al.*, MDCT correctly identified only 4/6 (66%) of pT3 renal pelvis UTUC. In examining overall accuracy in tumor stage prediction, the study quoted 87.8% (36/41), with a sensitivity of only 66.6% (8/12) for detection of invasion of UTUC into adjacent tissues.^[9] More recently, however, a study by Ng *et al.* determined a strong predictive value of preoperative hydronephrosis on three-dimensional imaging. In this study, when stratifying by preoperative hydronephrosis versus no hydronephrosis, the estimated 5-year recurrence-free survival was 56% vs. 41% ($P = 0.065$), metastasis-free survival was 86% vs. 62% ($P = 0.004$), and cancer-specific survival was 94% vs. 66% ($P = 0.001$).^[13]

Although the accurate diagnosis of UTUC extent has obvious implication if nephron-sparing surgery is contemplated, it also can affect the ultimate planning of surgical extirpation if the decision for NU has been made. Several studies have indicated the benefit for performing lymphadenectomy at time of surgery to improve disease specific survival. Roscigno *et al.* determined that nodal status is a significant predictor of disease specific survival and any patient expected to have pT2-pT4 tumors should undergo lymphadenectomy.^[18] Since pathologic stage is an important predictor of overall survival in UTUC, improved diagnosis of advanced disease

would allow for more consideration for a lymphadenectomy, although many argue that a lymphadenectomy should be performed during all NU procedures.

More accurate knowledge and understanding of stage may also delineate a role for neoadjuvant chemotherapy. Although limited data on chemotherapy for UTUC exist, a cisplatin-based regimen, as applicable for bladder cancer, can be extrapolated to advanced stage UTUC. For example, randomized phase III neoadjuvant cisplatin-based regimens for bladder cancer have shown survival benefits.^[19] Application of bladder cancer neoadjuvant chemotherapy regimens to UTUC would putatively show similar benefits because of the common occurrence of locally advanced UTUC disease at diagnosis.^[20] In fact, recently the group from MD Anderson has demonstrated both overall and disease-specific survival benefit in patients with high-risk UTUC treated with neoadjuvant cisplatin-based chemotherapy.^[21]

Our study suggests that radiographic analysis of UTUC patients does not always predict advanced stage of cancer. Our study showed 38.46% (10/26) patients with pT3 or greater disease had ipsilateral functional obstruction via radiographic analysis in comparison to 37.50% (21/35) patients with organ confined disease ($p=0.9334$). Thus, we cannot always rely upon functional renal obstruction as a prediction tool. This conclusion is in contrast to recent published studies correlating hydronephrosis and adverse pathologic features in NU for UTUC.^[13,14] Some differences in our study compared to these include the fact that we were not interested in only *hydronephrosis* but functional renal obstruction as defined by the criteria mentioned in the Methods section of this manuscript. Additionally, Messer et al. in their multi-institutional analysis found hydronephrosis to be an independent predictor for muscle invasive UTUC (pT2)^[14]; we instead were interested in predicting more advanced (\geq pT3) tumors.

Another important observation of this study was the location of tumor and the pathologic stage of UTUC in those patients who had functional renal obstruction. In our cohort, 7/10 (70%) of patients with pT3/T4 disease with functional renal obstruction had ureteral involvement while only 9/21 (42.9%) of patients with \leq pT2 disease and functional renal obstruction had ureteral involvement. Although not significant ($p=0.252$) this data suggest a trend towards advanced pathologic stage when a patient has radiographic evidence of functional renal obstruction caused by a ureteral tumor, as opposed to a renal tumor. This correlation was indeed found to be significant by Ng et al.^[13] However, the impact of tumor location on patient survival in UTUC has recently been called into question.^[22]

The pathophysiologic mechanism for our observation is not clear, although we do propose one possible mechanisms to explain functional renal obstruction as a marker of locally advanced disease, particularly in patients with a ureteral tumor. In the ureter, locally advanced tumors theoretically penetrate the muscularis propria, potentially diminishing peristaltic activity and thus causing obstruction, with hydronephrosis being the end result. Additionally, it has been our anecdotal experience that some advanced stage ureteral tumors present as dense strictures, proposing yet another mechanism for functional obstruction. For those with ipsilateral decrease in renal function and advanced stage, tumor location is shown in Table 5.

There are several limitations of our study, including its retrospective nature and incomplete data of all patients involved. Additionally, the disparity in relative renal function was set relatively arbitrarily, however the opinions of radiologists were sought for this purpose. Finally, a more ideal study design would involve a larger prospective evaluation with uniform preoperative imaging.

Conclusions

When considering only moderate correlation between pathologic tumor grade on biopsy and pathologic stage from NU specimen, and the shortcomings of other utilized modalities in determining locally-advanced disease, this study did not find that renal obstruction by radiographic analysis can always predict an advanced stage of UTUC. However, a trend was noticed towards advanced pathologic stage when patient had functional renal obstruction and a ureteral tumor. This can have a great clinical impact, providing guidance when deciding between nephron-sparing approaches versus extirpative management of the renal unit for UTUC, the need for lymphadenectomy, and identification of candidates for neoadjuvant chemotherapy or enrollment in clinical trials.

Disclosures

No competing financial interests exist for any of the authors.

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