A 20-Year Experience With Percutaneous Resection of Upper Tract Transitional Carcinoma: Is There an Oncologic Benefit With Adjuvant Bacillus Calmette Guérin Therapy?

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OBJECTIVES To determine whether there is an oncologic benefit of adjuvant bacillus Calmette Guérin (BCG) after resection of upper tract transitional cell carcinoma (UTTCC).

METHODS A total of 133 renal units (RU) treated by percutaneous resection for UTTCC between 1985 and 2005 were retrospectively analyzed. Forty-four RU were excluded because of carcinoma in situ, high grade/stage, metastatic disease present at initial presentation, and/or the patient could tolerate loss of RU. Eighty-nine RU treated primarily by percutaneous resection were then analyzed. Fifty RU received adjuvant BCG therapy 2 weeks after endoscopic management for a total of 6 courses. Recurrence was defined as a positive biopsy result after the third-look nephroscopy. Progression of disease was assessed at time of recurrence and defined as an increase in grade/stage of disease.

RESULTS Mean age (± SD) of 89 RU was 70.9 ± 11.1 years. Overall follow-up was 61.1 + 54.8 months. Grade distribution was 56.2% (50 of 89) and 43.8% (39 of 89) for low- and high-grade disease, respectively. There was no statistical difference with regard to tumor grade or stage between treated and nontreated groups ($P > .05$). Recurrence, time to recurrence, and progression of disease among RU treated with BCG were subselected by grade and compared with the corresponding nontreated group. Statistical significance between any of the treated and nontreated groups was not demonstrated ($P > .05$).

CONCLUSIONS Our data demonstrate that there is no overall oncologic benefit in the administration of adjuvant BCG with regard to disease recurrence, interval to recurrence, and progression of disease in the treatment of UTTCC. UROLOGY 73: 27–31, 2009. © 2009 Elsevier Inc.

Nephroureterectomy (NU) is considered the "gold standard" treatment for of upper tract transitional cell carcinoma (UTTCC). Kimball and Ferris[1] described the radical treatment of UTTCC in 1934. Since that time minimally invasive endoscopic techniques, including percutaneous surgery and ureteroscopy, have been perfected as alternative therapies with comparative oncologic outcomes when appropriately applied. The history of endoscopic management of UTTCC began in 1985 when Huffman et al[2] reported on a case treated with ureteroscopic resection. Shortly thereafter, Streem et al[3] published the first report of the percutaneous nephroscopic approach for the treatment of UTTCC.

In evaluating the efficacy of definitive endoscopic management of UTTCC, several outcomes need to be assessed, including tumor recurrence, tumor progression, renal preservation rate, overall survival, and cancer-specific survival. Because UTTCC occurs in 2%-5% of all urothelial tumors,[4] it is difficult to accrue a large series of patients or conduct treatment-based randomized trials.

MATERIAL AND METHODS

A retrospective analysis was performed at our institution of all patients treated primarily by percutaneous resection for UTTCC. Hospital and office charts for patients treated by a single surgeon (A.D.S.) were selected. The review encompassed all visits with the ICD-9 codes 189.0 (kidney, except pelvis) and 189.1 (renal pelvis), operative records for percutaneous

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Submitted: December 15, 2007, accepted (with revisions): June 1, 2008

0090-4295/09/$34.00
doi:10.1016/j.urology.2008.06.026

resection of urothelial carcinoma, and antegrade BCG V58.1 (encounter for chemotherapy and immunotherapy for neoplastic conditions).

A total of 125 patients (85 men and 40 women) comprising 133 renal units (RU) were treated by primary endoscopic intent (percutaneous resection) for UTTCC at our institution between April 1985 and October 2005. Four patients (4 RU) had carcinoma in situ (CIS) as the initial pathology and were excluded from the analysis. These patients with CIS were excluded because the benefit of BCG therapy has been previously reported.[5] Three patients (3 RU) were also excluded because of associated metastatic disease at initial presentation. Thirty-seven patients (37 RU) underwent definitive extirpative surgery shortly after initial attempt of endoscopic management (NU, distal ureterectomy). This was owing to patient choice and/or the presence of high-volume disease complicating the resection, the presence of a normal contralateral kidney, and the patient being able to tolerate the loss of a RU. These patients were not included in the final analysis because they no longer possessed a RU or ureter and therefore could not be placed in the surveillance protocol.

Eighty-nine RU were included in the final analysis. The initial indications for a nephron-sparing approach were bilateral UTTCC in 3 patients (3.4%), advanced age and other comorbidities in 17 patients (19.1%), a solitary kidney in 23 patients (25.8%), and elective in 46 patients (51.7%). Of 89 RU, 17 (19.1%) had a previous diagnosis of bladder cancer treated by transurethral resection and/or radical cystectomy with a urinary diversion before UTTCC resection.

Recurrence of tumor was assessed at the third nephroscopy, 3 months from the initial resection. Fifty RU received adjuvant BCG therapy with 81 mg of TheraCys (Sanofi Pasteur Inc., Swiftwater, PA) diluted into 50 mL of normal saline, given 2 weeks after endoscopic management for a total goal of 6 weekly treatments. All treatments were administered antegrade with a 14-F nephrostomy tube over 1 hour using manometry monitoring.[6] Tumor progression was defined as an increase in tumor stage and/or grade of any of the subsequent recurrences.

Our technique for percutaneous UTTCC resection has been described previously.[6] All patients underwent a metastatic workup that included abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), chest x-ray, liver function tests, and serum alkaline phosphatase level. If the latter was elevated, bone scintigraphy was performed.

All patients underwent a second-look nephroscopy within 1 week of resection to assess the previous resection and undergo reresection if needed before being placed in either treatment arm. Instillations of BCG began 2 weeks after the last resection. Prophylactic intravenous antibiotics were mandatory because the nephrostomy tubes invariably became colonized, creating a risk of urosepsis. An infusion of normal saline into the nephrostomy tube was started at 10 mL/h and increased 10 mL/h every hour to a target of 50 mL/h. Intrarenal pressure was closely monitored to ensure that it remained below 25 cm H_2O to prevent BCG dissemination due to obstruction. If the patient tolerated the saline infusion, 50 mL of 1×10^8 colony-forming units of BCG (81 mg of Theracys) was administered over 1 hour. Two weeks after completion of the 6 weekly treatments, a third-look nephroscopy was performed through the existing tract. Our criteria for BCG administration changed over the years on the basis of data from Memorial Sloan-Kettering.[7] Patients were counseled regarding the risks and possible benefits of adjuvant therapy, and a joint decision was made whether to undergo therapy. Therefore, this incorporates an inherent selection bias into our study.

Our surveillance protocol consisted of urine cytology and cystoscopy performed every 3 months for 1 year, biannually during the second year, and yearly thereafter. Ureteroscopy was performed at 6-month intervals for the first 3 years and annually thereafter. Upper tract imaging was performed annually with either retrograde or excretory pyelography, CT, or MRI.

RESULTS

Patient characteristics are as follows: the mean age (± SD) was 70.9 ± 11.1 years. Overall mean follow-up was 61.1 ± 54.8 months (median, 40.8 months). Grade distribution was 56.2% (50 of 89) and 43.8% (39 of 89) for low- and high-grade disease, respectively. Of 89 tumors, 15 (16.9%) were stage Tx, 45 (50.6%) Ta, 22 (24.7%) T1, 4 (4.5%) T2, and 3 (3.4%) T3. There were no statistically significant differences with regard to tumor grade or stage between BCG-treated and nontreated groups (Table 1).

Recurrence, recurrence-free survival, progression, renal preservation, incidence of bladder cancer, and overall survival among RU treated with BCG were subselected by grade and compared with the corresponding nontreated group (Table 1). In patients with initial low-grade disease, subsequent recurrences were treated with 4 percutaneous TCC resections, 8 NU, and 2 partial ureterectomies, with 1 patient undergoing palliative care for metastatic disease (lung). For high-grade disease, the treatments for recurrence were 9 percutaneous TCC resections and 4 NU, with 2 RU presenting with advanced metastatic disease (lung and liver). Patients with metastatic disease were categorized as failures with regard to renal preservation.

COMMENT

We report the largest retrospective series to date of patients undergoing minimally invasive treatment for UTTCC and adjuvant topical immunotherapy (BCG) and have applied the updated World Health Organization (WHO) criteria to the grading of TCC. In addition, all data calculations were also completed using the previous grading system and support the same conclusion drawn from the WHO classified data. Few institutions have expanded the indications from patients with bilateral tumors, Balkan nephropathy (predisposition to multiple tumors), solitary kidney, significant comorbidities, and renal insufficiency to include motivated, otherwise healthy patients with superficial low-grade disease who elect a nephron-sparing, minimally invasive approach.[8-10]

In our series, we found no difference between the BCG-treated and nontreated groups with regard to tumor grade (Table 1). Tumor grade was shown to be a statistically significant factor in overall survival when comparing grade of disease (a difference of 44.1 months; $P = .02$), yet the difference in recurrence-free survival was not found to be statistically significant ($P = .12$). Over-

Table 1. Data analysis of all patients, substratified by adjuvant therapy vs no adjuvant therapy

Parameter	No Adjuvant Therapy[a]	BCG Therapy[a]	*P* Value
Grade			.64
Low	23/50 (46)	27/50 (54)	
High	16/39 (41)	23/39 (59)	
Recurrence			
Low grade	6/23 (26)	9/27 (33)	.58
High grade	6/16 (38)	9/23 (39)	.91
Progression			
Low grade	4/23 (17)	4/27 (15)	.80
High grade	4/16 (25)	6/23 (26)	.94
Renal preservation			
Low grade	19/23 (83)	21/27 (78)	.67
High grade	13/16 (81)	20/23 (87)	.63
Overall survival (mo)			
Low grade	96.5	123.3	43 (log–rank)
High grade	68.0	68.1	.92 (log–rank)
Recurrence-free survival (mo)			
Low grade	101.94	103.96	.91 (log–rank)
High grade	40.79	68.81	.77 (log–rank)
Preoperative bladder cancer			
Low grade		9/50	
High grade		8/39	
Postoperative bladder cancer			
Low grade	8/23 (35)	4/27 (15)	.10
High grade	3/16 (19)	7/23 (30)	.44
De novo			
Low grade	5/23 (22)	3/27 (11)	.31
High grade	3/16 (19)	5/23 (22)	.82
Overall survival			
Low grade		116.4 mo	
High grade		72.3 mo	.02

BCG = bacillus Calmette-Guérin.
[a] Values in parentheses are percentages.

all, 15 of 50 (30%) RU with low-grade disease were assessed, and the mean time to recurrence was 33.8 ± 25.8 months. The renal preservation rate was 80% (40 of 50). There were no statistically significant differences in renal preservation rates reported in our series with respect to the treated and nontreated groups (Table 1).

High-grade UTTCC carries a poor prognosis, regardless of management modality. In the second-largest published series of grade 3 patients, Liatsikos et al, in an earlier series from this institution, reported 56% recurrence and 64% disease-specific survival.[11] In the present series, 15 of 39 patients (38%) with high-grade disease had a recurrence, with a mean of 20.5 ± 17.0 months to recurrence. Two of the 15 patients developed metastatic disease. The renal preservation rate was 84.6% (33 of 39).

The effect of stage on recurrence and disease-free survival can be seen in the study by Jabbour et al,[12] in which 54 patients were followed for a mean of 50 months after percutaneous resection of UTTCC. Stage Ta disease was associated with 30% recurrence and 93% disease-free survival, whereas T1 tumors recurred 57% of the time and were associated with a 64% disease-free survival rate. Stage retained its prognostic significance when stratified by grade.[12] The poorer prognosis of higher stage disease has been confirmed by other investigators. Patel et al[13] found that T1 had a higher recurrence rate than Ta (30% vs 12.5%). However, our most recent data do not support the previous series with regard to the incidence of Ta (13 of 45, 28.9%) and T1 (6 of 22, 27.3%) disease recurrence.

A final consideration is the risk of disease recurrence within the percutaneous tract, which was initially thought to be a significant hazard owing to the potential of tumor seeding the tract. Irradiation of the tract was used in 2 studies,[13,14] to avoid seeding in patients treated percutaneously. In our overall series (133 RU) there has been 1 case of tract seeding outside the 89 RU evaluated. Although there should always be concern to avoid nephrostomy tract tumor seeding, a 0.75% prevalence rate (1 of 133) in this large series may deem this event a rarity. Although this is our bias, our data support this notion.

A beneficial role for topical adjuvant therapy (BCG) after resection of papillary upper tract tumors has not been proven. No randomized trials of adjuvant therapy have been performed owing to the relative rarity of UTTCC. Even a multi-institutional effort would take years to reach any conclusions; however, such a trial would be useful in guiding therapy. To date, 5 series specifically assessing adjuvant BCG exist (Table 2). Recurrence rates range from 11% to 85%, although they are closer to 33%[15] in the second-largest series, which correlates with our overall recurrence rate of 36%. To date, there has only been 1 report comparing outcomes of patients who received postresection BCG with those who

Table 2. Recurrence rates after percutaneous resection of upper tract transitional carcinoma, stratified by tumor grade[a]

Series (Year)	Patients (n)	Mean Follow-Up (mo)	Mean Follow-Up to Recurrence	Grade 1[b]	Grade 2[b]	Grade 3[b]	Total[b]	Disease-Specific Survival (%)
Plancke et al[19] (1995)	10	28	7	1/6 (17)	0/30	0/1	1/10 (10)	100
Patel et al[13] (1996)	26	45	22	2/11 (18)	3/11 (27)	—	6/25[c] (24)	91
Liatsikos et al[11] (2001)[c]	69	49	NA	3/15 (20)	7/27 (26)	14/25 (56)	24/67 (36)	84
Palou et al[9] (2004)	34	51	24	12/28 (43)		3/5 (60)	15/34 (44.1)	94
Present series[c]	89	61	26	Low grade: 15/50 (30)		High grade: 15/39 (38)	30/89 (33)	—

[a] These series included patients treated with adjuvant chemotherapy.
[b] Values in parentheses are percentages.
[c] References overlap in patient data analysis.

did not, and it failed to show any benefit for grade 2 or 3 disease. However, our previous data reported a significantly lower recurrence rate in grade 2 patients receiving BCG (3 of 13) compared with those who received no adjuvant therapy (2 of 7); it is necessary to note that the sample size was extremely small.[16] Our most recent data regarding 89 RU treated with UTTCC percutaneous resections and 50 of 89 (56.2%) RU treated with adjuvant BCG immunotherapy revealed no statistical significance with regard to a decrease in progression or recurrence when stratified by grade or stage. In addition to not being randomized, this analysis lacked sufficient power to definitively exclude an advantage for any grade/stage of disease (Table 1). These recent findings therefore challenge the use of adjuvant immunotherapy.

The impact of initial grade, recurrence, and adjuvant BCG therapy on overall patient survival after UTTCC resection was assessed using the Kaplan-Meier analysis. The 5-, 10-, and 15-year overall survival rates were 57.8%, 46.8%, and 33.2%, respectively. When comparing the data with that from a smaller cohort from the Mayo Clinic, there is a similar overall survival, which may parallel the normal life expectancy of these patients (mean age, 70.8 years). Further analysis of the impact of initial grade on overall survival was assessed using the Kaplan-Meier test. There was a divergence in the overall survival of the different patient groups at 5 years: 69.2% and 42.1% for low-grade and high-grade disease, respectively ($P = .02$). Recurrence-free survival was not impacted by tumor grade ($P = .12$) (Table 1). Finally, adjuvant BCG therapy failed to show any difference in overall survival according to Kaplan-Meier analysis ($P = .52$). Unfortunately, cancer-specific survival could not be assessed for the entire cohort of patients; therefore it was not included in our analysis.

Complications associated with upper tract BCG instillation are rare: BCG dissemination and urosepsis secondary to gram-negative organisms. The exact number of treatments was identifiable in 28 of 50 patients (56%). The mean number of treatments was 5.4 in both the recurrence and nonrecurrence groups ($P = .87$). In our series there was 1 death due to sepsis, a testicular granuloma resulting in an orchiectomy, and 1 case of BCG dissemination. Fever has been reported in up to 67% of patients in one series,[17] and colonization of the nephrostomy tube with skin flora is frequent. Biopsies during post-BCG nephroscopy may reveal renal granulomas, but these generally have no clinical significance.[18]

Interestingly, our series of 89 RU included 23 (25.8%) solitary renal units. The recurrence rate for patients with a solitary kidney was 21% (5 of 23); recurrences were managed with 2 NU and 3 percutaneous TCC resections. Finally, the overall outcome was a 91.3% renal preservation rate (21 of 23), and no patients developed metastatic disease.

The large number of patients who were excluded immediately after the initial percutaneous resection (37

RU) had a negative metastatic workup. If at time of surgery the tumor was found to be multicentric, high volume, and/or the final pathology reported high-grade disease, they were deemed unsuitable for the surveillance protocol and scheduled for immediate extirpation (NU).

CONCLUSIONS

After nearly a quarter century, endourologic management of UTTCC is indicated and ideal for addressing low-grade papillary TCC limited to the renal calyces, pelvis, or the ureter. It is a current theme that endoscopic approaches are only good for low-grade disease; however, in this series the data imply that UTTCC resection is also a viable treatment for intermediate- and high-grade disease, with a minimum 80% renal preservation rate and a 92% renal preservation rate for patients with a solitary kidney. For those motivated patients with small, noninvasive, low-to-medium-grade disease, endourologic therapy provides a reasonable treatment option. In those patients with functionally solitary kidneys or a solitary kidney, conservative endourologic management of even high-grade disease may delay the need for nephrectomy, dialysis, and possible renal transplant.

A role for BCG in the treatment of upper tract CIS has been demonstrated; however, the definitive efficacy of adjuvant topical therapy after endoscopic resection of UTTCC has not been proven. Patient selection and long-term rigorous follow-up after endourologic treatment, especially with regular surveillance ureteroscopy, is critical to diagnose and treat recurrences in a timely manner and therefore maintain acceptable cancer-free survival rates.

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