Prognostic Factors in Transitional Cell Carcinoma of Upper Urinary Tract after Radical Nephroureterectomy

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A Dissertation Submitted to The Graduate School of Ajou University
in Partial Fulfillment of the Requirements for the Degree of
Master of Medicine

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February, 2011

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감사의 글

처음 대학원 과정에 입문할 때에는 막연히 '공부도 다 시기가 있어, 할 수 있을 때 해야지.' 라는 생각으로 시작했는데, 벌써 5년이라는 시간이 훌쩍 지나서, 이제야 결실을 맺으려고 합니다. 논문의 마무리를 글로 남기려 하니 지금까지 받기만 했던 제 자신을 보며 깊이 반성하게 됩니다.

비뇨기과에 들어와 모든 것이 서툴렀던 전공의 기간 중 석사학위취득이라는 것은 적지 않은 부담이었지만, 일련의 여러 과정들을 수행해 가며 많은 것을 배우고 경험할 수 있는 기회이기도 했습니다. 주변 여러 선생님들께서 도움을 주셨기에 가능했으리라 생각합니다. 찾아뵙고 인사드리지 못한 점, 이 짧은 분량의 글로 감사의 뜻을 전하는 점 미리 용서를 구합니다.

먼저 어렵게 꺼낸 논문주제변경이라는 얘기에 선뜻 외부에 있는 저를 배려해 주제를 변경해 주신 김세중 지도교수님, 바쁘신 와중에도 초라한 제 논문을 열과 성을 다해 심사해 주신 안현수 교수님, 주희재 교수님께 감사의 뜻을 전합니다.

그리고 이 논문이 완성되기까지 보이지 않는 곳에서 많은 도움을 주신 김선일 교수님, 조대성 선생님, 홍석영 선생님, 바쁜 전공의 과정동안 동시에 대학원 수업 참여, 여러 시험들을 수행해 갈 수 있도록 많은 격려와 조언을 아끼지 않으셨던 김영수 교수님, 최종보 교수님, 옆에서 함께 고생했던 비뇨기과 의국원들 모두에게 정말 감사하게 생각합니다.

마지막으로 부족한 남편이지만 항상 응원해 준 제 아내, 아무것도 모르지만 항상 믿고 따르는 두 아들들, 정신적으로, 경제적으로 언제나 지지해 주시는 부모님께도 감사의 마음 전합니다.

제가 아주대 비뇨기과에 들어와 만나게 된 모든 선생님들과의 소중한 인연은 정말 제 인생에 있어 더없이 큰 행운이라 생각하며, 이에 보답할 수 있는 사람이 되도록 항상 열심히 노력하겠습니다. 감사합니다.

2010년 12월

김 영 균

- ABSTRACT -

Prognostic Factors in Transitional Cell Carcinoma of the Upper Urinary Tract after Radical Nephroureterectomy

Purpose : The aim of this study was to evaluate the prognostic factors for survival in patients treated surgically for transitional cell carcinoma of the upper urinary tract (UUT-TCC).

Materials and Methods : I retrospectively reviewed the medical records of 87 patients (64 men and 23 women, mean age of 62.2 years) with UUT-TCC who had undergone radical nephroureterectomy at our institution between June 1994 and June 2009. The median follow-up period was 32 months. The prognostic significance of various clinicopathological variables for recurrence-free and cancer-specific survival was analyzed using univariate and multivariate analysis.

Results : Of total 87 patients, 21 patients (24.1%) developed local recurrence or distant metastasis and 16 patients (18.4%) died during the follow-up period. The 5-year recurrence-free and cancer-specific survival rates were 74.6% and 75.2%, respectively. On univariate analysis, hydronephrosis, T stage, N stage, and lymphovascular invasion (LVI) were significant prognostic factors for recurrence-free and cancer-specific survival. On multivariate analysis, T stage and LVI were independent prognostic factors for recurrence-free and cancer-specific survival.

Conclusions : The T stage and LVI are independent prognostic factors for recurrence-free and cancer-specific survival in patients with UUT-TCC

treated by radical nephroureterectomy. These findings would be helpful for guiding the decisions about adjuvant therapies and surveillance interval.

Key words : Urinary tract cancer, Transitional cell carcinoma, Prognosis

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I. INTRODUCTION

Transitional cell carcinoma of the upper urinary tract (UUT-TCC) is a relatively uncommon disease, accounting for 5-6% of all urothelial carcinomas. Radical nephroureterectomy with bladder cuff excision has been considered as the standard treatment for UUT-TCC (Oosterlinck et al, 2004). However, UUT-TCC is known to have a higher recurrence rate even after radical surgery, which may be due in part to the difficulty in early detection of the tumor, and the thinner muscular and submucosal layers and the absence of serosa in the upper urinary tract (Kang et al, 2003; Van der Poel et al, 2005).

Tumor stage, grade, and surgical procedure performed have been documented as the major prognostic factors in patients with UUT-TCC (Heney et al, 1981; Corrado et al, 1991; Hall et al, 1998; Hisataki et al, 2000). In addition, patient age, tumor size and architecture, tumor location, tumor multiplicity, lymphovascular invasion (LVI), and a previous history of bladder cancer have been suggested as the potential prognostic factors (Krogh et al, 1991; Hall et al, 1998; Oosterlinck et al, 2004; Kim et al, 2010). However, the influence of these potential prognostic factors for UUT-TCC remains less clear. A clear knowledge of these prognostic indicators of tumor recurrence and progression at the time of surgery would allow better prognostic evaluation and approach.

In this study, I retrospectively reviewed our single center experience in patients with UUT-TCC to identify the prognostic factors that predict recurrence-free and cancer-specific survival in patients with UUT-TCC after radical nephroureterectomy.

II. MATERIALS AND METHODS

I retrospectively reviewed the medical records of 87 patients (64 men and 23 women) who had undergone radical nephroureterectomy with bladder cuff excision for UUT-TCC at our institution between June 1994 and June 2009. Mean patient age was 62.2 years (range 33 to 85 years). None of the patients included in this study had distant metastasis at diagnosis. Regional lymph node dissection was performed in patients with clinically apparent lymphadenopathy on a preoperative radiologic imaging or in those who were suspected of having enlarged lymph nodes intraoperatively. Tumors were staged using the 2002 TNM staging system (Greene et al, 2002), and graded according to the World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading criteria (Epstein et al, 1998).

Hydronephrosis was assessed by preoperative imaging, and grade of hydronephrosis was estimated according to the methods described by Cho et al (Cho et al, 2007). The tumors without caliceal or pelvic dilation were classified as grade 0, tumors with pelvic dilation only as grade 1, tumors with mild caliceal dilation as grade 2, tumors with severe caliceal dilation as grade 3, and tumors with caliceal dilation accompanied by renal parenchymal atrophy as grade 4.

Patient follow-up were relatively uniform and included basic laboratory examinations, chest x-ray, cystoscopy, and urine cytology every 3 months for the first 2 years, every 6 months for the subsequent 2 years, and then yearly thereafter. Abdominopelvic computed tomography was performed annually during follow-up or when clinically indicated.

The 5-year recurrence-free and cancer-specific survival rates were analyzed. Disease recurrence was defined as local failure in the tumor bed, regional lymph nodes or distant metastasis. Because bladder recurrence did not affect survival in the patients with UUT-TCC, it was not considered in the analysis of recurrence-free survival rate.

Univariate and multivariate analyses were performed using the log-rank test and the Cox proportional hazards regression model, respectively. The prognostic factors assessed were age, gender, smoking history, previous history of bladder transitional cell carcinoma (TCC), concomitant bladder TCC, grade of hydronephrosis, body mass index (BMI), tumor location, tumor multiplicity, T stage, N stage, tumor grade, LVI, and squamous differentiation. All statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). The values of $p<0.05$ were considered to be statistically significant in all of the analyses.

III. RESULTS

The clinicopathological characteristics of the 87 patients with UUT-TCC are summarized in Table 1.

Table 1. Clinicopathological data of the 87 patients included in the study

Characteristics	No. of patients (%)
Age (years)	
≤65	46 (52.9)
>65	41 (47.1)
Gender	
Male	64 (73.6)
Female	23 (26.4)
Smoking history	
Smoker	57 (65.5)
Nonsmoker	30 (34.5)
Previous history of bladder cancer	
Absent	81 (93.1)
Present	6 (6.9)
Concomitant bladder cancer	
Absent	78 (89.7)
Present	9 (10.3)
Hydronephrosis	
0	27 (31.0)
1	1 (1.1)
2	25 (28.7)
3	19 (21.8)
4	15 (17.2)
Body mass index (BMI)(kg/m^2)	
<25	54 (62.1)
25-29.9	30 (34.5)
≥30	3 (3.4)
Tumor location	
Renal pelvis	48 (55.2)
Ureter	33 (37.9)
Both	6 (6.9)

Tumor multiplicity	
Single	81 (93.1)
Multiple	6 (6.9)
T stage	
Ta	15 (17.2)
T1	29 (33.3)
T2	12 (13.8)
T3	30 (34.5)
T4	1 (1.1)
N stage	
N0	77 (88.5)
N1	3 (3.4)
N2	6 (6.9)
N3	1 (1.1)
Grade	
Low	16 (18.4)
High	71 (81.6)
Lymphovascular invasion	
Absent	66 (75.9)
Present	21 (24.1)
Squamous differentiation	
Absent	82 (94.3)
Present	5 (5.7)

The primary tumor was located in the renal pelvis, ureter, or both in 48 (55.2%), 33 (37.9%), and 6 (6.9%) patients, respectively. Six patients (6.9%) had a previous history of bladder TCC and 9 patients (10.3%) had concomitant bladder TCC when the UUT-TCC was diagnosed. On the preoperative imaging studies, 60 patients (69.0%) presented with ipsilateral hydronephrosis. The grade of hydronephrosis was 1, 2, 3, and 4 in 1 (1.1%), 25 (28.7%), 19 (21.8%), and 15 (17.2%) patients, respectively.

The median follow-up period was 32 months (mean 42.9, range 1 to 131 months). Of total 87 patients, 21 patients (24.1%) recurred,

including 7 with local recurrence and 14 with distant metastasis. The site of local recurrence was retroperitoneal or pelvic lymph nodes and distant metastasis occurred in lung, liver, bone, contralateral adrenal gland, sigmoid colon, or pelvic side wall. Sixteen patients (18.4%) died during the follow-up period.

The 5-year recurrence-free survival rate was 74.6%. The univariate analysis identified that grade of hydronephrosis (p<0.001), T stage (p<0.001), N stage (p=0.001), and LVI (p<0.001) were significant prognostic factors for recurrence-free survival, whereas the multivariate analysis indicated that T stage (p=0.011) and LVI (p=0.011) were independent prognostic factors (Table 2).

Table 2. Univariate and multivariate analysis of potential prognostic factors for recurrence-free survival

Variables	Univariate	Multivariate	
	p-value	Hazards ratio (95% CI)	*p-value*
Age (≤65 vs. >65 years)	0.272	1.667 (0.600-4.631)	0.327
Gender (Male vs. Female)	0.772	0.928 (0.212-4.066)	0.921
Smoking history (No vs. Yes)	0.980	1.583 (0.407-6.157)	0.507
Previous history of bladder cancer (No vs. Yes)	0.608	0.798 (0.163-3.902)	0.780
Concomitant bladder cancer (No vs. Yes)	0.557	1.512 (0.288-7.940)	0.625
Hydronephrosis (G0-G2 vs. G3+G4)	<0.001	0.194 (0.017-2.224)	0.187

BMI (<25 vs. 25-29.9 vs. ≥30 kg/m^2)	0.389	1.598 (0.756-3.377)	0.219
Tumor location (Renal pelvis vs. Ureter)	0.826	0.681 (0.196-2.362)	0.545
Tumor multiplicity (Single vs. Multiple)	0.469	0.788 (0.143-4.357)	0.785
T stage (Ta-T2 vs. T3+T4)	<0.001	21.762 (2.007-235.966)	0.011
N stage (N0 vs. N1-N3)	0.001	0.670 (0.169-2.654)	0.569
Tumor grade (Low vs. High)	0.066	2.714 (0.287-25.646)	0.384
Lymphovascular invasion (No vs. Yes)	<0.001	5.770 (1.505-22.123)	0.011
Squamous differentiation (No vs. Yes)	0.887	0.554 (0.051-6.036)	0.628

BMI: body mass index

The 5-year cancer-specific survival rate was 75.2%. The univariate analysis revealed that grade of hydronephrosis (p=0.001), T stage (p<0.001), N stage (p<0.001), and LVI (p<0.001) were significant prognostic factors for cancer-specific survival, whereas multivariate analysis demonstrated that T stage (p=0.006), and LVI (p=0.010) were independent prognostic factors (Table 3).

Table 3. Univariate and multivariate analysis of potential prognostic factors for cancer-specific survival

Variables	Univariate	Multivariate	
	p-value	Hazards ratio (95% CI)	*p-value*
Age (≤65 vs. >65 years)	0.197	3.378 (0.780-14.637)	0.104
Gender (Male vs. Female)	0.618	0.563 (0.068-4.689)	0.596
Smoking history (No vs. Yes)	0.433	1.564 (0.292-8.384)	0.601
Previous history of bladder cancer (No vs. Yes)	0.417	1.438 (0.229-9.043)	0.699
Concomitant bladder cancer (No vs. Yes)	0.183	2.369 (0.296-18.959)	0.416
Hydronephrosis (G0-G2 vs. G3+G4)	0.001	0.079 (0.004-1.406)	0.084
BMI (<25 vs. 25-29.9 vs. ≥30 kg/m^2)	0.070	2.126 (0.785-5.760)	0.138
Tumor location (Renal pelvis vs. Ureter)	0.833	0.702 (0.137-3.612)	0.672
Tumor multiplicity (Single vs. Multiple)	0.815	0.369 (0.038-3.595)	0.391
T stage (Ta-T2 vs. T3+T4)	<0.001	57.234 (3.192-1026.223)	0.006
N stage (N0 vs. N1-N3)	<0.001	1.500 (0.281-8.006)	0.635
Tumor grade (Low vs. High)	0.112	1.731 (0.121-24.671)	0.686
Lymphovascular invasion (No vs. Yes)	<0.001	10.040 (1.727-58.383)	0.010
Squamous differentiation (No vs. Yes)	0.942	1.286 (0.084-19.791)	0.857

BMI: body mass index

IV. DISCUSSION

Although recent literature suggests that endourological techniques for UUT-TCC have been associated with the preservation of renal function in selected cases, nephroureterectomy with bladder cuff excision is still the standard treatment with the highest cancer-specific survival (Hall st al, 1998). However, UUT-TCC shows a significantly high local failure even after radical surgery, especially in patients with high stage and grade tumors (Heney et al, 1981). Because the location of the UUT-TCC may hinder early detection, UUT-TCC is more likely to be diagnosed as invasive cancers compared to bladder cancers. Anatomical differences between bladder and ureter or renal pelvis wall also account for differences in the higher incidence of invasive UUT-TCC. The thickness of the bladder wall is estimated to exceed that of ureteral wall 2-3 fold (Yang and Huang, 2003). The distal ureter is covered by 3 muscular layers, whereas the more proximal part of the ureter only contains 2 relatively thin interlacing layers (Hanna et al, 1976). Urothelial cancer invasion may be correlated with muscular wall thickness (Van der Poel et al, 2005). Therefore, this fact indicates the importance of surgical competence and adequate adjuvant therapy in patients with high risk for failure of UUT-TCC and other potential prognostic factors to predict high risk group of UUT-TCC should be identified.

It has been suggested that the factors such as T stage, tumor grade, tumor location, lymph node involvement, LVI, and surgical procedure performed were associated with the prognosis (Heney et al, 1981; Krogh et al, 1991; Hall st al, 1998; Kikuchi et al 2005; Hong et al,

2005; Roscigno et al, 2008; Kim et al, 2010). T stage and tumor grade probably were the best established major prognostic factors in UUT-TCC. 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 (Hall et al, 1998).

With regard to the tumor grade, 5-year cancer-specific survival rates were reported from 90% to 100% for low grade UUT-TCC, and from 28% to 46% for high grade UUT-TCC (Lee et al, 1996; Akdogan et al, 2006). Moreover, a few studies indicated the independent prognostic role of tumor grade (Kang et al, 2003; Akdogan et al, 2006), insisting that patients with high-grade cancers had at least 2-fold increased risk of cancer-related death compared to those with low-grade tumors. However, my study failed to prove the independent prognostic role of tumor grade, which was consistent with the results of other large series (Hall et al, 1998; Van der Poel et al, 2005; Hong et al, 2005).

Several other putative factors have been proposed with sometimes conflicting results. One of the major issues in UUT-TCC is the prognostic role of a previous history of bladder cancer and concurrent bladder cancer. A previous history of bladder cancer was identified in approximately 7% of my cases and from 9% to 20% of patients in other studies (Hall et al, 1998; Akdogan et al, 2006). In my analysis, a previous history of bladder cancer did not show the prognostic significance for UUT-TCC. However, Mullerad et al reported that a history of bladder cancer was an independent predictor of cancer-specific survival in multivariate analysis (Mullerad et al, 2004).

Conversely, Rabbani et al reported that de novo UUT-TCC had a 1.67-fold increased risk of cancer-related death compared with UUT-TCC after bladder cancer in the multivariate analysis and they emphasized the prognostic importance of concurrent bladder cancer more than previous bladder cancer history (Rabbani et al, 2001). Kang et al reported that the presence of concurrent bladder cancer at the moment of the treatment for UUT-TCC, mostly by nephroureterectomy, was an independent predictor of cancer-specific survival (Kang et al, 2003). However, my study did not show any relationship between concurrent bladder cancer and recurrence-free or cancer-specific survival.

With regard to the tumor location, some studies reported that patients with cancers arising from the renal pelvis have a better cancer-related survival than those with cancers in the ureter, and tumor site is an independent predictor of cancer-specific survival (Park et al, 2004; Akdogan et al, 2006). Such results may be explained by the presence of a thin layer of adventitia surrounding the ureter, which contains an extensive plexus of ureteral blood vessels and lymphatics that makes tumor invasion easier. The other possible reason is that the renal parenchyma and perihilar adipose tissue surrounding the renal pelvis may act as a barrier against early spread (Hanna et al, 1976; Miyake et al, 1998). Conversely, van der Poel et al demonstrated that patients with tumors in the renal pelvis and proximal ureter were 2.5 times more likely to die of disease compared to those with tumors in the distal ureter (Van der Poel et al, 2005). In my series, there was no significant difference in recurrence-free or cancer-specific survival between renal pelvis and ureteral cancers.

Novara et al demonstrated that tumor multiplicity within the

UUT-TCC was an independent predictor of cancer-specific survival (Novara et al, 2007). The authors suggested that these features strongly reconfirmed the panurothelial nature of the disease along with the prognostic role of prior or concomitant bladder cancers. In my series, however, tumor multiplicity was predictive of neither recurrence-free nor cancer-specific survival, which was in agreement with other reports which failed to demonstrate a significant prognostic role of multiplicity in UUT-TCC (Kang et al, 2003; Mullerad et al, 2004).

The presence of LVI has been reported to be an important prognostic factor in UUT-TCC (Hong et al, 2005; Kikuchi et al, 2005; Kim et al, 2010). Kim et al demonstrated that LVI was an independent prognostic factor for recurrence-free and cancer-specific survivals in patients with localized UUT-TCC after nephroureterectomy (Kim et al, 2010). Hong et al also suggested LVI as an independent prognostic factor for recurrence-free survival in patients with UUT-TCC (Hong et al, 2005). LVI was also an independent predictor of recurrence-free and cancer-specific survivals in my series.

Preoperative hydronephrosis has also been reported as an important predictor of UUT-TCC. Cho et al found that the grade of hydronephrosis and the tumor diameter correlated with the pathologic T stage and had a significant influence on prognosis of UUT-TCC (Cho et al, 2007). Brien et al demonstrated that preoperative evaluation for hydronephrosis could identify patients at risk for advanced UUT-TCC and such knowledge might impact extent of surgery as well as the need for perioperative chemotherapy regimens (Brien et al, 2010). However, my study failed to prove the independent prognostic role of

preoperative hydronephrosis.

My study had several limitations. It was retrospective in nature and the size of the study population is smaller than the recently reported multicenter study because I collected our single center experience of the uncommon disease. The follow-up period may not be long enough. Nevertheless, I believe that the results of my study will support the already established T stage and LVI as independent prognostic factors for recurrence-free and cancer-specific survival in patients with UUT-TCC treated by radical nephroureterectomy.

V. CONCLUSION

The results of this study have demonstrated that T stage and LVI are independent prognostic factors for recurrence-free and cancer-specific survival in patients with UUT-TCC treated by radical nephroureterectomy. These findings would be helpful for guiding the decisions about adjuvant therapies and surveillance interval.

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– 국문요약 –

근치적 신요관전적출술을 시행받은 상부요로 이행세포암에서 예후인자

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목적 : 상부요로 이행세포암은 비교적 드문 암으로 최근에 진단기술의 발달, 환경적 요인 및 노령 인구의 증가 등으로 인해 발생률이 증가하고 있다. 상부요로 이행세포암은 방광암에 비해 예후가 나쁜 것으로 알려져 있으나 병기 및 분화도 외에는 아직 예후인자에 대한 연구는 제한적이다. 이에 본 연구에서는 근치적 신요관적출술을 시행받은 상부요로 이행세포암에서 여러 임상병리학적 변수를 분석하여 예후와의 연관성을 알아보고자 하였다.

대상과 방법 : 1994년 6월부터 2009년 6월까지 본원에서 상부요로 이행세포암으로 근치적 신요관전적출술을 시행받은 환자 중 추적관찰이 가능하였던 87명 (남자 64명, 여자 23명, 평균연령 62.2세)을 대상으로 하였으며, 중간 추적관찰 기간은 32개월이었다. 단변량 및 다변량 분석을 이용하여 무재발 및 암특이 생존율에 대한 다양한 임상병리학적 변수들의 예후인자로서의 가치를 알아보았다.

결과 : 전체 87명 환자 중 21명 (24.1%)에서 국소재발 혹은 원격전이가 발생하였고, 16명 (18.4%)이 추적관찰 기간 도중에 사망하였다. 5년 무재발 생존율과 암특이 생존율은 각각 74.6%와 75.2%였다. 단변량 분석에서는 무재발 및 암특이 생존율에 대해 수신증, T 병기, N 병기 및 림프관/혈관 침범이 통계학적으로 유의한 예후인자였다. 다변량 분석에서는 무재발 및 암특이 생존율에 대해 T병기 및 림프관/혈관 침범 여부만이 독립적인 예후인자였다.

결론 : T병기 및 림프관/혈관 침범여부는 근치적 신요관전적출술을 시행받은 상

부요로 이행세포암 환자에서 무재발 및 암특이 생존율에 대한 독립적인 예후인자로 나타났다. 이러한 소견은 보조적 치료 및 추적관찰 기간의 간격 등을 결정하는데 도움을 주리라고 생각한다.

핵심어 : 상부요로 이행세포암, 근치적 신요관적출술, 예후