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Low-level Ki-67 expression as an independent predictor of bladder tumour recurrence in patients with primary upper tract urothelial carcinoma after radical nephroureterectomy

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Abstract

Objective: To evaluate the association of molecular markers and conventional clinicopathological factors with bladder tumour recurrence in patients with primary upper tract urothelial carcinoma after radical nephroureterectomy.

Methods: The expressions of Ki-67 and P53 were measured by immunohistochemical staining prospectively in 115 consecutive patients with primary upper tract urothelial carcinoma from March 2004 to February 2014. The Cox proportional hazards regression model was used to identify independent predictors. The association between Ki-67 expression and clinicopathological variables was assessed by the χ^2 test.

Results: Intravesical recurrence occurred in 13 out of 115 (11.3%) patients with a mean follow-up of 54.2 months (range: 7–130). Low-level Ki-67 expression ($P = 0.010$), older age (>65, $P = 0.040$) and lower ureter tumour ($P = 0.001$) were independent predictors of bladder tumour recurrence in Cox regression analysis. Ki-67 expression was elevated with the progression of tumour grade ($P = 0.004$) but not with stage ($P = 0.186$). Ki-67 overexpression was also significantly higher in aggressive pathological types ($P = 0.008$), but only shows an inclination towards poor oncologic outcomes in the cancer-specific survival rate ($P = 0.107$) and the overall survival rate ($P = 0.063$).

Conclusions: Low-level Ki-67 expression was an independent predictor for bladder tumour recurrence, while Ki-67 overexpression was associated with adverse clinicopathological parameters and poor prognosis in patients with primary upper tract urothelial carcinoma after radical nephroureterectomy.

Key words: bladder tumour, nephroureterectomy, Ki-67 expression, predictor, upper tract urothelial carcinoma

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease accounting for ~5–10% of all urothelial carcinomas in Western countries (1,2). Up to 23–47.2% of patients may develop bladder tumour after radical nephroureterectomy (RNU) (3–5). Previously, few available methods could prevent bladder tumour recurrence. Up to date, randomized controlled trial studies showed that a single dose of intravesical instillation following RNU appeared to reduce the risk of developing a bladder cancer, with a low risk of complications (6,7). However, at least one-half of the patients do not have recurrence of bladder tumours in the subsequent years, especially in primary UTUC, and so there may be over-treatment.

In 2014, Xylinas et al. (8) developed nomograms for predicting intravesical recurrence, which could improve the clinical decision-making process with regard to cystoscopic surveillance schedules and postoperative intravesical instillations of mitomycin-C after RNU. However, incorporating biologically significant biomarkers into those nomograms may allow us to counsel patients more accurately (9).

As is known, Ki-67 and P53 were well-studied and promising biomarkers for urothelial tumours (10,11). Ki-67 is a nuclear protein representing cell proliferation that is particularly active in malignant tumours. P53 is a tumour suppressor gene involved in genomic stability, gene repair and cell apoptosis. Particularly, Ki-67 overexpression was shown to be associated with worse oncologic outcomes in UTUC (12). Here, we evaluated the role of molecular markers Ki-67 and P53 as well as conventional clinicopathological factors as predictors of bladder tumour recurrence in patients with primary UTUC.

Patients and methods

We reviewed all the records of 115 patients with primary UTUC after RNU from March 2004 to February 2014 in Beijing Hospital of the Ministry of Health. Lymphadenectomy was performed only in patients with suspicious lymph node invasion on imaging or intraoperative inspection, as the majority of lymph nodes cannot be assessed. None of those patients received neo-adjuvant chemotherapy, while 10 patients received adjuvant chemotherapy and 9 patients received radiotherapy for advanced stage. In the intravesical chemotherapy group, 11 patients received a single dose of intravesical instillation and 16 patients received at least four doses of chemotherapy weekly.

Follow-up mainly consisted of physical examination, urine cytology, chest X-ray, and abdominal ultrasound and computed tomography or magnetic resonance urography. Cystoscopy was suggested every 3 months for the first 2 years, every 6 months for the next 2 years and annually thereafter. All patients were followed retrospectively both through hospital records and by telephone interviews, either with the patients or their offspring. We assessed local recurrence in the retroperitoneum or renal fossa and distant metastasis. Bladder tumour recurrence was considered a secondary malignancy.

Tumour stage was assessed according to the UICC (Union for International Cancer Control) tumour node metastasis classification of malignant tumours 2004. Tumour grading was assessed according to the World Health Organization classification of 2009.

Immunohistochemistry (IHC) staining for molecular markers Ki-67 and P53 was performed prospectively by pathologists and described routinely in pathology reports. Pathological characteristics were reassessed by a genitourinary pathologist. The percentage of Ki-67 positive cells was visually counted in 500 cells of the hotspots at high magnification and the Ki-67 value was scored by the labelling index. According to the recommendation of Krabbe et al. (12), low-level Ki-67 expression was defined as staining of 20% or less and high-level Ki-67 expression was defined as staining of >20%. P53

Table 1. Patient and tumour characteristics

Variables	*N*	%
Patients	115	100.0
Gender		
Male	57	49.6
Female	58	50.4
Age		
≤65	43	59.7
>65	72	40.3
Tumour side		
Right	57	49.6
Left	58	50.4
Operation		
Open	61	53.0
Laparoscopic	54	46.9
Urinary cytology		
Positive	84	73.0
Negative	31	27.0
Intravesical chemotherapy		
No	88	76.5
Yes	27	23.5
Multiplicity		
Solitary	94	81.7
Multiple	21	19.3
Tumour site		
Calix or pelvis	55	47.8
Upper + mid ureter	24	20.9
Lower ureter	24	20.9
>1 site	12	10.4
Pathology		
UC	94	81.7
UC and NV + SA	7	6.1
UC and CIS + AC + SCC	13	11.3
Tumour stage		
Tis	1	0.9
Ta-T1	34	29.6
T2	39	33.9
T3–T4	41	35.7
Nodal status		
PNo-Nx	109	94.8
PN+	6	5.2
Tumour grade		
Low	47	40.9
High	67	58.3
NA	1	0.9
Adjuvant chemotherapy		
No	105	91.3
Yes	10	8.7
P53		
–	38	33.0
+	28	24.3
++	19	16.5
+++	24	20.9
NA	6	5.2
Ki-67		
≤20%	48	41.7
>20%	59	51.3
NA	8	7.0

UC, urothelial carcinoma; NV, nerve and vessel invasions; SA, sarcoma; CIS, carcinoma *in situ*; AC, adenocarcinoma; SCC, squamous cell carcinoma; NA, not available.

Table 2. Univariate and multivariate analysis of factors associated with bladder tumour recurrence in patients with primary UTUC after RNU

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Conventional clinicopathological factors						
Gender (male/female)	0.606	0.198–1.855	0.380			
Age (≤65/>65)	2.151	0.592–7.819	0.245	4.198	1.065–16.547	0.040*
Left/right	2.288	0.704–7.434	0.169			0.732
Open/laparoscopic	1.471	0.493–4.391	0.489			–
Urinary cytology (negative/positive)	1.088	0.299–3.956	0.898			–
Instillation (no/yes)	1.019	0.280–3.705	0.977			–
Solitary/multiple	0.833	0.184–3.764	0.812			–
Tumour location			0.008*			0.004*
Calix or pelvis			1.000			1.000
Upper + mid ureter	0.734	0.076–7.061	0.789	0.743	0.077–7.182	0.798
Lower ureter	7.217	1.902–27.383	0.004*	10.097	2.495–40.864	0.001*
>1	1.519	0.158–14.605	0.717	2.460	0.246–24.558	0.443
Tumour stage			0.283			0.510
Ta-T1			1.000			1.000
T2	1.567	0.459–5.354	0.474			0.603
T3–T4	0.447	0.082–2.443	0.353			0.248
Tumour grade (low/high)	1.301	0.424–3.990	0.646			0.489
Adjuvant chemotherapy (no/yes)	1.003	0.130–7.719	0.998			–
Biomarkers						
Ki-67 (>20%/≤20%)	3.903	1.056–14.421	0.040*	5.858	1.528–22.451	0.010*
P53			0.657			0.891
–			1.000			1.000
+	0.953	0.269–3.379	0.941			0.669
++	0.800	0.161–3.967	0.785			0.850
+++	0.261	0.031–2.168	0.214			0.467

HR, hazard ratio; CI, confidence interval.
*Statistical difference.

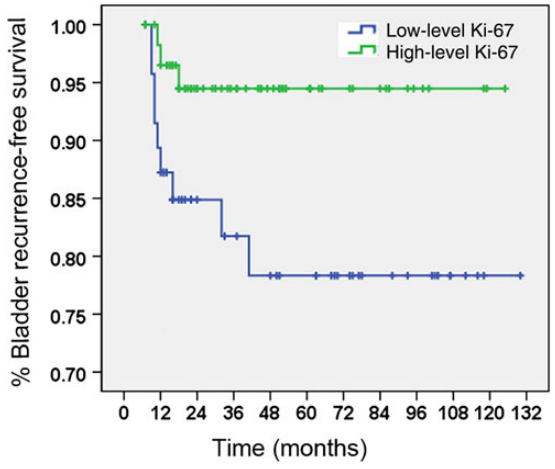

Figure 1. Kaplan–Meier plot shows bladder tumour recurrence-free survival curves stratified by Ki-67 expression ($P < 0.05$).

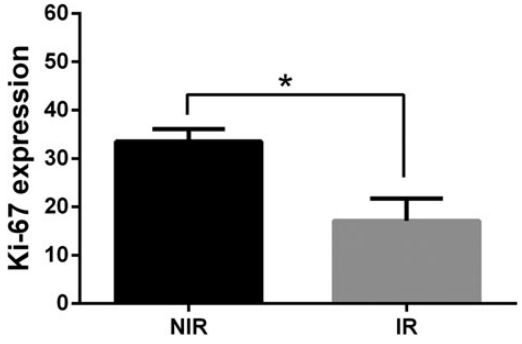

Figure 2. Difference of Ki-67 expression between intravesical recurrence or not in upper tract urothelial carcinoma tissue ($P < 0.05$). NIR, no intravesical recurrence; IR, intravesical recurrence. *$P < 0.05$.

expression was defined as four categories in the pathology report: – for negative, + for mild, ++ for moderate and +++ for strong (10).

All analysis was done with SPSS version 16.0 (IBM Corp., Armonk, NY, USA). All reported *P* values are two sided, and a *P* value of <0.05 was considered statistically significant. Univariate and multivariate analyses were used by the Cox proportional hazard regression model. The association of Ki-67 and clinicopathological variables was assessed by the Pearson test and the χ^2 test.

Results

Low-level Ki-67 expression as an independent predictor of bladder tumour recurrence

A total of 115 patients with primary UTUC were included in this cohort. The mean age was 66.7 years (range: 32–85). Table 1 lists patient and tumour characteristics. Intravesical recurrence of bladder cancer occurred in 13 out of 115 (11.3%) patients. The mean follow-up time was 54.2 months (range: 7–130).

To analyse the risk factors affecting bladder tumour recurrence in patients with primary UTUC after RNU, univariate and multivariate analyses of conventional clinicopathological factors and molecular

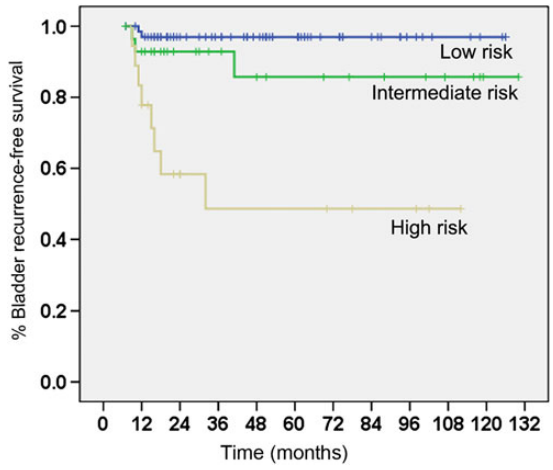

Figure 3. Kaplan–Meier plot shows bladder tumour recurrence-free survival curves stratified by risk group ($P < 0.001$).

markers associated with bladder tumour recurrence are described in Table 2. In univariate analyses, tumour location and low-level Ki-67 expression (Fig. 1) were significantly associated with bladder tumour recurrence. We also found that the mean values of Ki-67 were 35.5 ± 2.6% in the group without intravesical recurrence, while they were 17.1 ± 4.6% in the group with intravesical recurrence ($P < 0.05$, Fig. 2). The median values of Ki-67 expression were 35% (1–90%) and 15% (1–50%) in those two groups, respectively. Multivariate Cox proportional hazards regression analyses were performed, adjusted for age, tumour side, tumour stage, tumour grade, tumour location and expressions of P53 and Ki-67. Multivariate analysis revealed that low-level Ki-67 expression ($P = 0.010$), advanced age (>65 years, $P = 0.040$) and lower ureter ($P = 0.001$) were significant risk factors for bladder cancer recurrence-free survival.

According to the coefficients to construct the risk stratification, we defined three risk groups. The low-risk group was no risk factor or included one risk factor such as older age (>65 years) or low-level Ki-67 expression; the intermediate-risk group was only with lower ureter tumours, and older age with low-level Ki-67 expression; and the

Table 3. Association of Ki-67 and P53 expression with clinicopathological parameters in 107 patients with primary UTUC after RNU

Variables	Ki-67 expression		*P*	P53 expression				*P*
	Low level	High level		–	+	++	+++	
Patients	48	59	–	38	28	19	24	–
Gender			0.281					0.848
Male	27	27		20	15	8	13	
Female	21	32		18	13	11	11	
Age			0.312					0.600
≤65	20	19		17	10	6	7	
>65	28	40		21	18	13	17	
Tumour side			0.515					0.615
Right	25	27		22	13	9	10	
Left	23	32		16	15	10	14	
Urinary cytology			0.290					0.589
Positive	34	47		27	22	12	19	
Negative	14	12		11	6	7	5	
Multiplicity			0.628					0.547
Solitary	40	47		30	25	14	20	
Multiple	8	12		8	3	5	4	
Tumour site:			0.153					0.237
Calix or pelvis	28	24		20	16	8	8	
Upper + mid ureter	8	13		4	7	4	7	
Lower ureter	10	13		9	5	3	7	
>1	2	9		5	0	4	2	
Pathology			0.008*					0.786
UC	45	42		29	24	17	19	
UC + NV + SA	1	5		4	1	0	2	
UC + CIS + AC + SCC	1	12		5	3	2	3	
Tumour stage			0.186					0.976
Ta-T1	17	15		12	9	5	6	
T2	18	18		12	10	6	10	
T3–T4	13	26		14	9	8	8	
Nodal status			0.559					0.902
PNo-NX	46	55		36	27	18	22	
PN+	2	4		2	1	1	2	
Tumour grade			0.003*					0.003*
Low	26	16		24	9	4	6	
High	21	43		14	19	15	17	
Ki-67 expression			–					0.008*
≤20%	–	–		22	16	3	6	
>20%	–	–		16	12	12	18	

*Stand for statistical difference.

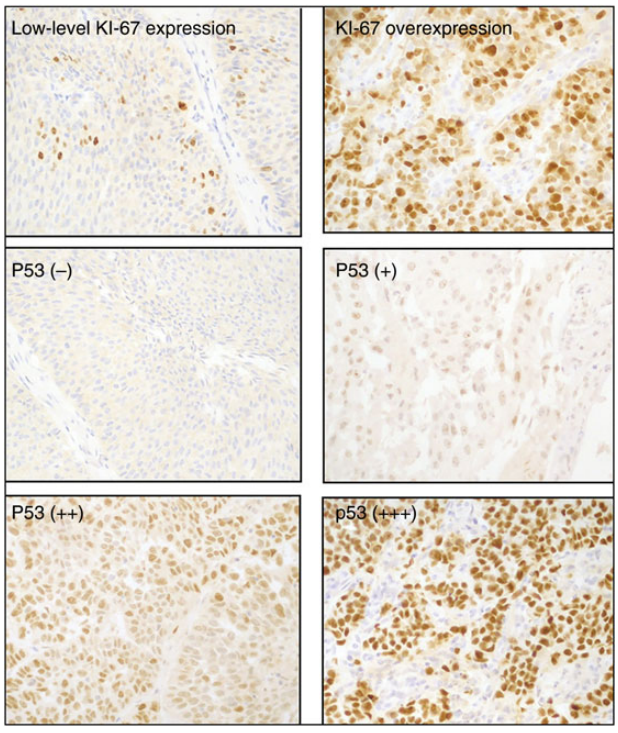

Figure 4. Immunohistochemical staining of Ki-67 and P53 expression in upper tract urothelial carcinoma tissue (×200).

high-risk group was with lower ureter tumours concurrent with older age (>65 years) or/and low-level Ki-67 expression. There was a significant difference ($P < 0.001$) between these three groups in bladder tumour recurrence-free survival, as shown in Fig. 3.

Ki-67 overexpression was associated with worse clinicopathological parameters and poor oncological outcomes

Association of Ki-67 expression with clinicopathological parameters is summarized in Table 3. Ki-67 expression was low level in 48 patients (44.9%), but 59 patients (55.1%) showed Ki-67 overexpression. Ki-67 expression was elevated with the progression of tumour grade ($P = 0.004$) but not with stage ($P = 0.186$). Ki-67 expression was also significantly higher in aggressive pathological types ($P = 0.008$).

Further analysis was done to explore the relationship between Ki-67 expression and oncological outcomes. There were 17 patients (14.8%) with progression and 17 deaths (14.8%) including 14 who died of UTUC during follow-up. In Fig. 4, Kaplan–Meier analysis revealed no significant differences in recurrence free survival (RFS) rates ($P = 0.235$) between low-level Ki-67 expression and overexpression. However, compared with low-level Ki-67 expression, Ki-67 overexpression were predisposed to poor cancer specific survival (CSS) ($P = 0.017$), as shown in Fig. 5.

Discussion

In the present study, we investigated conventional clinicopathological factors as well molecular markers Ki-67 and P53 expression as risk factors of bladder cancer recurrence in primary UTUC after RNU. To our knowledge, the present study is the first one in this era that found that low-level Ki-67 expression could be regarded as an independent

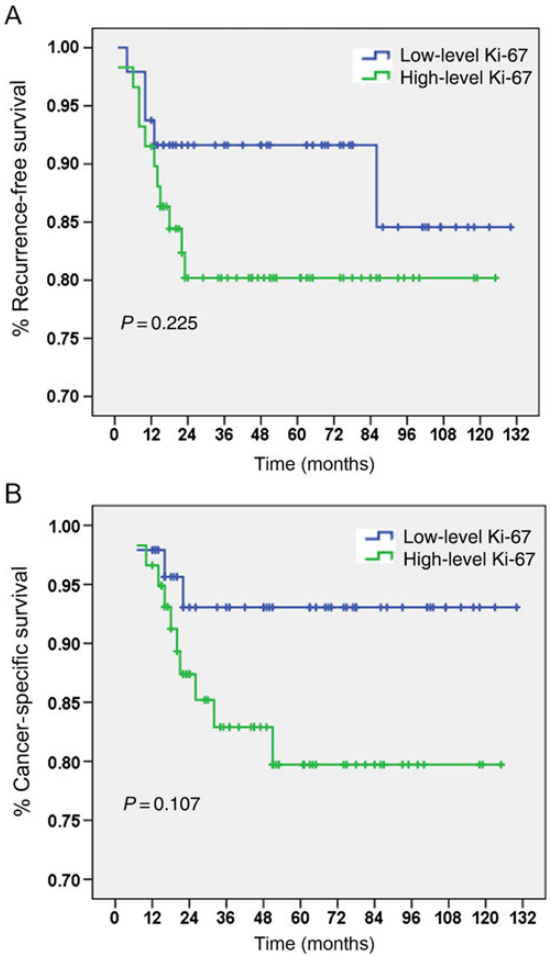

Figure 5. (A) Kaplan–Meier plot shows recurrence-free survival curves. (B) Cancer-specific survival curves.

predictor of intravesical recurrence in patients with UTUC after RNU. We found that Ki-67 overexpression was associated with advanced tumour grade and inclined towards poor prognosis, just as previous studies. In addition, advanced age and lower ureter were independent predictors of bladder cancer recurrence in multivariate analyses.

As is known, Ki-67 overexpression was associated with high grade and poor prognosis in urothelial tumours, which was observed in many works in the literature (13–16). In our 107 patients, we found that Ki-67 expression was elevated with the progression of tumour grade ($P = 0.004$) and aggressive pathology ($P = 0.008$). The largest series to date, reported by Jeon et al. (17) on 107 UTUC patients, revealed that Ki-67 overexpression was an independent risk factor for RFS as well as CSS, whereas Fromont et al. (18) and Feng et al. (10) found that there was no correlation between CSS and Ki-67 overexpression. However, our study only showed that Ki-67 overexpression is closely related to poor CSS.

Using a relatively large sample size in the univariate and the multivariate model, we found that a low-level Ki-67 labelling index was an independent predictor of bladder cancer recurrence after RNU. The paradox is why low-level Ki-67 is associated with a high rate of recurrence in primary UTUC, while Ki-67 overexpression is related to a high rate of bladder tumour recurrence in non-muscle invasive bladder cancers (19). It is pointed out that although urothelial carcinoma of the bladder and UTUC share many characteristics, they are disparate twins and represent

two distinct diseases (20). Fang et al. (21) proved that low grade was an independent risk factor for bladder cancer recurrence in primary UTUC in a large Chinese population. They were, however, also confused about their results. When these two papers are considered together, we found that the results have an internal consistency: Low-grade tumour was associated with a low level of Ki-67 expression as shown in our study. However, Narukawa et al. (22) found that high-grade tumour predicted intravesical recurrence after nephroureterectomy in UTUC patients. Another Chinese scholar found there was no relationship between Ki-67 and bladder cancer recurrence in 88 UTUC patients, because some patients who receive neoadjuvant chemotherapy were included and patients with concomitant/previous bladder cancers were not excluded.

The predictive value of age and tumour location has been proved in some large sample studies. Compared with pelvic tumours, ureteral tumour location is an independent predictor associated with bladder tumour recurrence (8,23). The study by Fang and our study found that lower ureter is an independent risk factor for bladder tumour recurrence in the Chinese population, maybe because of the reason that lower ureter tumours are adjacent to the bladder and can easily invade the mucosa. Age had been used in the nomograms developed by Xylinas et al. (8) for prediction of intravesical recurrence after RNU. The more advanced the age, the greater is the risk for bladder tumour recurrence in UTUC patients.

Some limitations of this study should be considered. Firstly, this was a retrospective study containing some bias. Secondly, the bladder recurrence rates in our study were relatively lower than those in previous studies, which is partly due to prophylactic intravesical instillation and excluding high-risk patients with contamination/previous bladder tumours (24–26). Thirdly, our centre evaluated Ki-67 and P53 expression prospectively, with limitations on consistency and with the reproducibility of IHC questionable. More importantly, small sample size limited the ability to distinguish outcomes further. Despite these limitations, our research was with a relatively large sample size, combining molecular markers to find out predictive factors for bladder tumour recurrence in primary UTUC after RNU.

In conclusion, biomarker Ki-67 expression gives us valuable prognostic information on patients with primary UTUC after RNU. Low-level Ki-67 expression, just like conventional risk factors of advanced age and lower ureteral tumour, could be regarded as an independent predictor for intravesical tumour recurrence, while Ki-67 overexpression is associated with advanced tumour grade and was inclined towards poor prognosis. Multi-centre studies are needed to evaluate the role of Ki-67 expression in predicting bladder tumour recurrence, which will contribute to develop more comprehensive nomograms for individualized bladder surveillance and prophylactic intravesical chemotherapy in primary UTUC after RNU.

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Conflict of interest statement

None declared.

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