

Glomerular Filtration Rate' Prognostic Potential

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Tumors originating in urothelial cells, including ureter to renal pelvis, are known as upper tract urothelial carcinomas (UTUCs).

Keywords: prognosis ; upper urinary tract ; urothelial carcinoma ; renal function ; renal insufficiency

1. Introduction

UTUCs are rare malignant tumors that account for approximately 5–10% of all urothelial cancers [1][2][3]. Radical nephroureterectomy (RNU) with bladder cuffing represents the ultimate treatment for highly recurrent UTUC [4][5]. In previous studies, the classification of five-year cancer-specific survival (CSS) was based on pathologic stages. The 5-year CSS exceeded 90% when the final pathological result was pT1 (non-muscle invasive cancer) or less. However, the 5-year CSS decreased to 40% when the pathological result was pT3 or higher [6]. This finding suggests that RNU is sufficient for organ-confined early-stage UTUC, whereas RNU alone is insufficient for non-organ confined advanced UTUC with non-organ confined or lymph node metastasis. Complete lymph node dissection along with RNU can increase CSS in patients with UTUCs (pT3 or higher) [7][8][9][10]. Other studies reported that adjuvant chemotherapy with locally advanced UTUC (pT3N0/Nx, pT4N0/Nx, or pTanyN+) can effectively increase CSS [11]. Based on the findings of previous studies, locally advanced UTUCs are an indication for lymph node dissection and adjuvant chemotherapy.

Several prognostic factors for UTUC have been reported. Postoperative pathological parameters such as pathologic tumor stage (pT), lympho-vascular invasion (LVI), tumor grade, tumor necrosis, lymph node (LN) involvement, surgical margin, and histological variants are strong prognostic factors. Preoperative prognostic factors include the presence of hydronephrosis, serum CRP, tumor size, tumor location, history of previous bladder cancer, age, Eastern Cooperative Oncology Group performance status (ECOG PS), and chronic kidney disease (CKD) [12][13][14][15][16][17][18][19][20][21]. However, most of the studies reporting various prognostic factors were retrospective in design.

CKD is a common disease diagnosed in the elderly population. It is associated with malignancies of kidney and ureter [22][23]. The underlying treatment for UTUC is radical resection of the kidney, leaving the patient with a unilateral kidney for survival after surgery. As the unilateral kidney after the surgery needs to perform the function of both kidneys, the patient's renal function might be reduced compared with the level before the surgery, which could result in CKD and affect survival [24][25]. Renal function is particularly important in patients with locally advanced UTUC because of the need for adjuvant chemotherapy after surgery.

2. Estimated Glomerular Filtration Rate as a Prognostic Factor

Ito et al. [2] analyzed 70 patients with N0M0 UTUC who underwent unilateral RNU between 1999 and 2012. The survival rate was expressed as a 3-year extraurothelial recurrence-free survival rate (EURFS). In the multivariate Cox proportional hazards model, the EURFS had a worse outcome in patients with a preoperative eGFR less than 60 mL/min/1.73 m² (HR: 6.579, 95% CI: 1.934–22.222, $p = 0.0026$). Yeh et al. [26] investigated the postoperative prognosis according to the presence of preoperative hydronephrosis and flank pain in 472 UTUC patients who underwent RNU in a single medical center from 1991 to 2013. The survival rate was expressed as 5-year CSS and 5-year OS using the Kaplan–Meier method. The eGFR was set at 60 mL/min/1.73 m². Those with preoperative hydronephrosis and flank pain had worse outcomes of 5-year CSS and 5-year OS, respectively. Since preoperative hydronephrosis and flank pain were associated with preoperative renal function, patients with eGFR less than 60 mL/min/1.73 m² before surgery had worse outcomes of 5-year CSS (HR: 1.691, 95% CI: 1.071–2.669, $p = 0.024$) and 5-year OS (HR: 1.577, 95% CI: 1.045–2.382, $p = 0.030$). Ehdiaie et al. [27] developed a model to predict the prognosis of 253 patients who underwent RNU for UTUC between 1995 and 2008. A multivariable Cox regression model was used and eGFR was set as a continuous variable. Survival rates were expressed as 5-year CSS and 5-year PFS. The higher the preoperative eGFR, the better was the 5-year PFS (HR: 0.73, 95% CI: 0.61–0.88, $p < 0.001$) and 5-year CSS (HR: 0.74, 95% CI: 0.61–0.90, $p = 0.002$).

These preceding studies showed that preoperative renal function was positively correlated with CSS, PFS, and OS of patients with UTUC. However, Xylinas et al. [28] showed no association between preoperative renal function and survival rate of patients with UTUC who underwent RNU. Xylinas et al. investigated 781 patients with UTUC treated with RNU from 1994 to 2007 at seven different centers. The preoperative eGFR criterion was set at 60 mL/min/1.73 m², and the postoperative eGFR criterion was set at 45 mL/min/1.73 m². Univariable and multivariable Cox regression models were used. Neither preoperative nor postoperative eGFR was associated with 5-year CSS, PFS, or OS. In our systematic review and meta-analysis, eight studies demonstrated a relationship between PFS and preoperative eGFR (adjusted HR: 1.51, 95% CI: 1.23–1.80, $p < 0.00001$). In five studies, PFS and preoperative eGFR showed a significant positive correlation. Although one study showed a positive correlation and two studies showed a negative correlation, all three studies showed no significant correlations. Nine studies showed a relationship between CSS and preoperative eGFR. Although one study showed a negative correlation between CSS and preoperative eGFR and two studies showed a positive correlation, none of them showed statistically significant correlation between CSS and preoperative eGFR. The remaining six studies showed a significant positive relationship between the two (adjusted HR: 1.63, 95% CI: 1.38–1.92, $p < 0.00001$). Seven studies showed a relationship between OS and preoperative eGFR. Although one study showed a negative relationship, the correlation was not significant. Six studies showed a positive relationship between OS and preoperative eGFR. However, only three studies showed significant correlation between the two variables (adjusted HR: 1.22, 95% CI, 1.10–1.35, $p < 0.00001$). Results of this study confirmed that the preoperative renal function of patients was closely related to their survival rate after RNU.

Several previous studies have shown that renal function decreases after kidney surgery [28][29][30]. Although patients who underwent radical nephrectomy had severe renal impairment more than those who underwent partial nephrectomy, the rate of CKD was increased postoperatively in patients with partial nephrectomy [31]. In addition, UTUC patients who underwent radical nephrectomy had significantly higher serum creatinine increase and higher rates of ESRD hemodialysis than those of RCC patients (HR: 2.9, 95% CI: 1.88–4.49, $p < 0.001$) [29]. Some studies have shown that patients with CKD or ESRD exhibited a lower survival rate than that of those with normal renal function [24][25]. If UTUC patients manifest reduced preoperative renal function, they carry a high probability of developing CKD or ESRD due to their decreased renal function after radical nephrectomy-based RNU. Therefore, it can be inferred that they will have poor outcomes such as disease prognosis and survival rate.

Patients with non-organ-confined or lymph node metastasis undergoing UTUC require adjuvant chemotherapy because it is impossible to perform surgical treatment. Adjuvant chemotherapy for UTUC basically entails a combination of gemcitabine and cisplatin [32][33]. Cisplatin-induced nephrotoxicity is well known [34][35]. When cisplatin is absorbed into renal tubular cells, it can trigger an inflammatory response via multiple signaling pathways, leading to histological damage. Cisplatin also affects renal vessels and causes ischemic damage [36]. Therefore, patients with reduced renal function cannot use cisplatin-based chemotherapy and, thus, exhibit a worse survival rate.

3. Conclusion

In conclusion, patients with decreased eGFR before surgery manifested poor PFS, CSS, and OS after RNU. Thus, a large-scale prospective study is needed in the future.

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