Ph.D. Dissertation of Medicine

Prognostic role of estimated glomerular filtration rate in upper tract urothelial carcinoma: A systematic review and meta-analysis

상부요로 요로상피암에서 추정 사구체 여과율의 예후변수 역할: 체계적 문헌고찰 및 메타분석

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Abstract

Background

Preoperative renal function could be associated with worse outcomes of patients who have undergoing a radical nephro-ureterectomy (RNU). The purpose of this study was to determine the association of preoperative renal function with the oncological outcome of patients who underwent RNU through a systematic review and meta-analysis.

Materials and Methods

We searched articles published up to March 2021 in PubMed, Scopus, and Embase by combining "urothelial carcinoma", "radical nephroureterectomy", and "estimated glomerular filtration rate". We also manually screened the reference list for publications following general guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The category of survival was expressed as overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS).

Results

This study included a total of 4,668 patients who received RNU from 13 studies. Pooled analysis showed that patients with decreased preoperative renal function before surgery manifested poor PFS, CSS, and OS after RNU.

Conclusion

For upper tract urothelial carcinoma (UTUC) patients who received RNU, there was a significant association of decreased preoperative renal function with poor survival. However, the studies included in this study were all retrospective studies. Therefore, a large-scale prospective study is needed in the future to confirm the finding of this study.

Keyword : prognosis, upper urinary tract, urothelial carcinoma, renal function, renal insufficiency

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Introduction

Tumors originating from urothelial cells, including ureter to renal pelvis, are called upper tract urothelial carcinomas (UTUCs). UTUCs are rare malignant tumors that account for about 5-10% of all urothelial cancers. (1-3) Radical nephro-ureterectomy (RNU) with bladder cuffing is the ultimate treatment because of a high recurrence rate of UTUC.(4, 5) In previous studies, five-year cancer specific survival (CSS) was divided based on pathologic stages. When the final pathological result was pT1 (non-muscle invasive cancer) or less, the 5-year CSS exceeded 90%. However, when the pathological result was pT3 or higher, the 5-year CSS decreased to 40%.(6) This means 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. For UTUCs of pT3 or higher, complete lymph node dissection along with RNU can increase CSS.(7-10) In other studies, adjuvant chemotherapy with locally advanced UTUC (pT3N0 / Nx, pT4N0 / Nx, or pTanyN (+) can effectively increase CSS.(11) Based on findings of previous studies, locally advanced UTUC should undergo lymph node dissection and adjuvant chemotherapy.

Several UTUC prognostic factors have been reported. Postoperative pathological results such as pathologic tumor stage (pT), lympho-vascular invasion (LVI), tumor grade, tumor necrosis, lymph node (LN) involvement, positive surgical margin, and histological variant feature are strong prognostic factors. Preoperative prognostic factors include presence of hydronephrosis, serum C –reactive protein (CRP), tumor size, tumor location, history of previous bladder cancer, age, Eastern Cooperative Oncology Group performance status (ECOG PS), and chronic kidney disease (CKD).(12-21) Although many studies have reported various prognostic factors, most of them are retrospective studies.

CKD is a common disease in the elderly population. It is associated with kidney and ureter malignancies.(22, 23) The underlying treatment for UTUC is to radically remove the kidney, forcing the patient to live on a unilateral kidney after surgery. As the unilateral kidney after the surgery needs to perform functions of both kidneys, renal function of the patient might be reduced compared to that before the surgery, which could result in CKD and affect survival.(24, 25) Renal function is particularly important to locally advanced UTUC patients because they need adjuvant chemotherapy after a surgery. Although many studies have shown that CKD is a significant preoperative prognosis factor of UTUC, most of these studies have limitations due to their retrospective nature. Therefore, the objective of this study was to analyze associations of preoperative renal function with postoperative survival using a systematic review and meta-analysis.

Materials and Methods

This study was conducted and reported in accordance with the general guidelines recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for systematic review and meta-analysis.(26) We reviewed studies involving participants who underwent RNU for upper tract urothelial carcinoma, including open laparoscopic and robotic surgical interventions.

Data sources and search strategy

The PRISMA flow chart is shown in Figure 1. We searched PubMed, Scopus, and Embase for related articles published before March 2021. The following search terms and their combinations were used: "urothelial carcinoma", "radical nephroureterectomy" and "estimated glomerular filtration rate". We also manually screened the reference list of publications to find potentially relevant studies for analysis.

Inclusion and exclusion criteria

We used strict inclusion and exclusion criteria to limit the heterogeneity of the entire study. If the study met the following including criteria, it was eligible for additional evaluation: (1) it included patients who had been diagnosed with urothelial carcinoma by pathological evaluation; (2) the relationship between preoperative renal function and prognosis was evaluated; and (3) sufficient information was included to estimate the hazard ratio (HR) and 95% confidence interval (CI).

The exclusion criteria were as follows: (1) letters, comments, case reports, reviews, and conference abstracts with limited data; (2) publications in languages other than English; (3) studies performed using animals or cell lines; and (4) duplicate articles and articles with duplicate data. If the same patient population was evaluated in several studies, only the latest or the largest study was included in the analysis. Studies that did not report adjusted HR using multivariate analysis were excluded because the accuracy of HR without multivariate analysis was uncertain. For studies that applied both multivariate and univariate analyses to estimate clinical outcomes, results of the multivariate analysis were used to calculate HR and CI. Each study was independently screened by two reviewers (MHK and JHK) to determine if they met the selection criteria. Any disagreement was resolved by consensus. Finally, thirteen papers(7, 11, 22, 27-36) were included in this study.

Data extraction

Two investigators (HDY and CWJ) reviewed each eligible article individually and extracted information from all publications that met the inclusion criteria. Information was retrieved based on the Reporting recommendations for tumor MARKer prognostic studies (REMARK) guidelines for reporting prognostic markers. The data table was configured to extract all relevant data for each study text, table, or figure contained. Any disagreement was resolved through discussions.

Quality assessments

Methodological quality of each study was evaluated independently by three reviewers (MHK, CK and HHK) using the Newcastle-Ottawa scale (NOS) for including cohort studies only. (Table 6) A maximum score of 1 was assigned to each item and a maximum score of 2 was allowed only for comparability. Therefore, the final quality score varied from 0 (the lowest) to 9 (the highest) and a total score of 0–5 was considered low, 6–7 was considered intermediate, and 8–9 was considered high quality.

Statistical analysis

Survival data were synthesized using the event occurrence time HR for operating measurements. The HR and 95% CI were calculated with a random effect model. Forest plots were used to estimate the effect of estimated glomerular filtration rate (eGFR) on patient survival and disease progression. A statistical test of heterogeneity was performed based on the Cochran Q-test and I^2 test to assess heterogeneity during the study.(37) A p-value > 0.05 and an I^2 < 50% were considered non-heterogeneous. Potential publication bias was assessed through visual inspection of the funnel plot. Statistical significance was defined at the 0.05 level. All statistical analyses were performed using RevMan 5.4.1 software (Cochrane Collaboration, Cochranehagen).

Results

Individual characteristics of 13 studies are shown in Table 1. The recruitment period was from 1991 to 2017. The number of patients included in these studies was between 70 and 666, with a total number of 4,668. All 13 were retrospective studies. Of them, eleven, two, and eleven studies mentioned inclusion/exclusion criteria, definition of survival, and definition of eGFR, respectively. Ten out of thirteen papers were for Asians, five from Japan, three from Taiwan, one from Korea, and one from China. The remaining three papers included two from a multination and one from the United States.

Table 2 shows patient characteristics of each paper. Median age ranged from 67 to 74 years. Three studies did not indicate age. In nine studies, a surgical approach was indicated. Open approach was used for 2,031 cases and laparoscopic approach was used for 2393 cases. The median follow-up period was 16 to 65 months.

Table 3 and Table 4 show tumor characteristics and pathologic characteristics, respectively. Ten studies showed tumor location. There were 1,830 tumors in the renal pelvis and 1,783 tumors in the ureter. In 9 studies, a total of 656 people received adjuvant chemotherapy. In eleven studies, tumor grade was low in 1335 (31%) cases and high in in 2950 (69%) cases. The pathologic T stage was shown in nine studies, including 2,381 (60%) below pathologic T2 and 1,577 (40%) above pathologic T3.

Table 5 shows results of multivariate analyses using the cox proportional hazards model. Survival analysis were expressed as overall survival (OS), progression-free survival (PFS), or cancer-specific survival (CSS). The standard of eGFR was set at 30 ml/min/1.73m^2 in one paper, 50 ml/min/1.73m^2 in two studies, and 60 ml/min/1.73m^2 in the rest of studies.

Figure 2 shows a forest plot and a funnel plot to demonstrate PFS according to preoperative renal function. Eight studies were included and showed significant associations of worse PFS with decreased preoperative renal function (adjusted HR: 1.51; 95% CI: 1.23–1.80, $p < 0.00001$). The chi-squared p-value representing heterogeneity was 0.006, and the I^2 value was 64%. The funnel plot was relatively symmetrical, showing no evidence of a significant publication bias.

Nine studies showed a relationship between CSS and preoperative renal function. The forest plot and funnel plot are shown in Figure 3. Studies showed a significant correlation of poor CSS with decreased preoperative renal function (adjusted HR: 1.63, 95% CI: 1.38–1.92, $p < 0.00001$). The chi-squared p-value was 0.02, and the I^2 value was 56%. In funnel plots, studies tended to be skewed to the right of the center, but it did not show strong evidence for a publication bias.

Seven studies showed a relationship between OS and preoperative renal function. Forest plots and funnel plots are shown in Figure 4. Studies showed a significant relation of low OS with decreased preoperative renal function (adjusted HR: 1.22, 95% CI: 1.10–1.35, $p < 0.00001$). The chi-squared p-value was 0.08, the I^2 value was 46%, which was less than 50%.

In funnel plots, each study was close to the center and evenly present on both sides.

As mentioned above, since the eGFR standards of the articles included in this study are different, a subgroup analysis was performed with the articles based on 60 ml/min/1.73m^2. All articles showing the relationship between OS and preoperative renal function were based on eGFR 60 ml/min/1.73m^2. However, 1 article in PFS and 2 articles in CSS had different criteria of eGFR, so their articles were excluded. Seven studies showed significant associations of worse PFS with decreased preoperative renal function (adjusted HR: 1.60; 95% CI: 1.33–1.91, p <0.00001)(Supplementary 1). The chi-squared p-value representing heterogeneity was 0.03, and the I^2 value was 57%. Seven studies showed a significant correlation of poor CSS with decreased preoperative renal function (adjusted HR: 1.52, 95% CI: 1.27–1.81, p < 0.00001) (Supplementary 2). The chi-squared p-value was 0.04, and the I^2 value was 54%. The funnel plots for PFS and CSS were relatively symmetrical, showed no significant publication bias.

Discussions

This study investigated whether renal function of UTUC patients before RNU had an association with their survival rate. Thirteen studies were included. The total number of patients was 4668. All patients were diagnosed with UTUC. They underwent RNU. Each paper expressed the survival rate as CSS or PFS or OS. The final meta-analysis showed that preoperative renal function was related to postoperative survival rate.

Ito et al. (7) studied 70 N0M0 UTUC patients 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 the patient group with a preoperative eGFR lower than 60 ml/minute/1.73 m^2 (HR: 6.579, 95% CI: 1.934-22.222, $p = 0.0026$). Yeh et al. (35) studied 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. The Kaplan–Meier method was used. The eGFR was set at 60 ml/minute/1.73 m^2. 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 lower than 60 ml/minute/1.73 m^2 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, $p = 0.030$). Ehdaie et al. (38) studied a model predicting prognosis of 253 patients who underwent RNU as 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 the 5-year RFS (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 decreased preoperative renal function was correlated with worse CSS, PFS, and OS of patients with UTUC. However, Xylinas et al. (28) showed no association between preoperative renal function and survival rate of UTUC patients who underwent RNU. Xylinas et al. studied 781 patients who underwent RNU from 1994 to 2007 with UTUC at 7 multi-centers. The preoperative eGFR criterion was set at 60 ml/minute/1.73 m^2 and the postoperative eGFR criterion was set at 45 ml/minute/1.73 m^2. Univariable and multivariable Cox regression models were used. Neither preoperative nor postoperative eGFR showed association with 5-year CSS, PFS, or OS.

Although two studies showed a reverse correlation between PFS and preoperative renal function, eight studies demonstrated a significant relationship between poor PFS with decreased preoperative eGFR (adjusted HR: 1.51, 95% CI: 1.23–1.80, $p < 0.00001$). Nine studies showed a relationship between CSS and preoperative eGFR. Although one study showed a reverse correlation between CSS and preoperative eGFR, pooled analysis showed a significant relationship of low CSS with decreased preoperative eGFR (adjusted HR: 1.63, 95% CI: 1.38–1.92, $p < 0.00001$). Seven studies showed a relationship between OS and preoperative eGFR. Although only three studies showed significant correlations between OS and preoperative eGFR, pooled analysis showed a significant correlation between worse OS and decreased preoperative eGFR (adjusted HR: 1.22, 95% CI, 1.10–1.35, $p < 0.00001$). Results of this study confirmed that the decreased preoperative renal function of patients was closely related to their worse survival rate after RNU.

Several previous studies have shown that renal function decreases after kidney surgery.(28, 39, 40) Although patients who underwent radical nephrectomy had more severe renal impairment than those who underwent partial nephrectomy, the rate of CKD was increased postoperatively in patients with partial nephrectomy.(41) In addition, UTUC patients who underwent radical nephrectomy had significantly higher serum creatinine increase and higher rates of end stage renal disease (ESRD) hemodialysis than RCC patients (HR: 2.9, 95% CI: 1.88-4.49, $p < 0.001$).(40) Some studies have shown that patients with CKD or ESRD have a lower survival rate than those with normal renal function.(24, 25) If UTUC patients have reduced preoperative renal function, they have a high probability of developing CKD or ESRD due to their decreased renal function after RNU. Therefore, it can be inferred that they will have poor outcomes such as disease prognosis and survival rate.

Non-organ confined or lymph node metastasis UTUC patients require adjuvant chemotherapy because it is impossible to perform surgical treatment for them properly. Adjuvant chemotherapy for UTUC is basically performed with a gemcitabine-cisplatin combination.(42, 43) Cisplatin-induced nephrotoxicity is well known.(44, 45) When cisplatin is absorbed into renal tubular cells, it can cause an inflammatory response through several signaling pathways, leading to histological damage. Cisplatin could also affect renal vessels and cause ischemic damage.(46) For the above reasons, patients with reduced renal function cannot use cisplatin-based chemotherapy. Thus, it can be inferred that they will have a worse survival rate.

Our systematic review and meta-analysis study have several limitations. First, ten out of thirteen papers were for Asians. These ten papers included five from Japan, three from Taiwan, one from Korea, and one from China.(7, 22, 27, 29, 30, 32-36) The remaining three papers included two from a multination and one from the United States.(11, 28, 31) Regarding the number of patients, there were 3,343 Asians, 245 Americans, and 1,080 multination. Thus, Asians accounted for at least 71% of all subjects. Since Asians were included in the study performed in the United States and multination, there was a limit to sufficiently evaluate other races. Second, all thirteen papers included in this study had limitations as they were retrospective studies. However, most of these studies had an adequate sample size and a NOS quality score of 6 or higher. Finally, there was heterogeneity between papers. The I^2 value indicating heterogeneity exceeded 50% (PFS, 64%; CSS, 56%). Thus, a careful approach is needed to analyze results of this study.

Conclusion

In conclusion, this systematic review and meta-analysis study showed that patients with decreased eGFR before surgery had poor results of PFS, CSS, and OS after RNU. However, all studies included in this meta-analysis were retrospective in nature. Thus, a large-scale prospective study is needed in the future.

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Abstract in Korean

배경

수술 전 불량한 신장 기능은 근치적 신요관 절제술을 받은 환자의 더 좋지 않은 종양학적 결과와 관련될 수 있다. 본 연구의 목적은 체계적 문헌고찰 및 메타분석을 통해 근치적 신요관 절제술을 받은 환자의 수술 전 신장 기능과 종양학적 결과의 연관성을 확인하는 것이다.

방법

"요로상피암", "근치적 신요관 절제술" 및 "추정 사구체 여과율"을 조합하여 2021년 3월까지 PubMed, Scopus 및 Embase에 게재된 논문들을 검색했다. 또한 PRISMA 가이드라인에서 권장하는 지침에 따라 본 연구에 포함될 논문들을 연구자들이 직접 선별했다. 본 연구에서는 생존율을 전체 생존율, 무진행 생존율 및 암 특이적 생존율로 세분화하여 분석하였다.

결과

이 연구에는 13개의 연구에서 근치적 신요관 절제술을 받은 총 4,668명의 환자가 포함되었다. 메타 분석을 통해 무진행 생존율 (위험률: 1.51, 95% 신뢰구간: 1.23–1.80, p <0.00001), 암 특이적 생존율 (위험률: 1.63, 95% 신뢰구간: 1.38–1.92, p <0.00001) 그리고 전체 생존율 (위험률: 1.22, 95% 신뢰구간: 1.10–1.35, p <0.00001) 모두 수술 전 신장 기능이 낮은 환자일수록 생존율이 좋지 않다는 결과를 보여주었다.

결론

근치적 신요관 절제술을 시행 받은 상부 요로상피암 환자에서 수술 전 감소된 신장 기능은 좋지 않은 생존율과 연관성이 있다.

주요어: 예후, 상부요로, 요로상피암, 신기능, 신부전

학번: 2021-35049

Table 1. Main characteristics of the eligible studies

Study	Year	Country	Recruitment period	No. of patients	Prospective data collection	Inclusion/exclusion criteria	Consecutive patients	Definition of survival	Definition of eGFR
Xylinas	2013	Multination	1994-2007	666	No	Yes	NA	Yes	Yes
Ito	2014	Japan	1999-2012	70	No	Yes	NA	No	Yes
Raman	2014	Multination	2003-2012	414	No	No	NA	No	Yes
Morizane	2015	Japan	2000-2012	345	No	Yes	NA	Yes	No
Yeh	2015	Taiwan	1991-2013	472	No	Yes	NA	No	Yes
Huang	2016	Taiwan	2001-2016	198	No	Yes	NA	No	Yes
Xing	2016	China	2000-2013	192	No	Yes	NA	No	Yes
Yu	2017	Korea	2004-2014	566	No	Yes	NA	No	Yes
Koguchi	2018	Japan	1990-2015	433	No	Yes	NA	No	Yes
Freifeld	2019	USA	1993-2016	245	No	Yes	NA	No	No
Jan	2019	Taiwan	2007-2017	424	No	Yes	NA	No	Yes
Kuroda	2019	Japan	1999-2017	187	No	No	NA	No	Yes
Momota	2019	Japan	1995-2017	456	No	Yes	NA	No	Yes

eGFR: estimated glomerular filtration rate, NA: not available

Table 2. Patient characteristics of the eligible studies

Study	Median age, range (years)	Gender (male/female)	Median BMI, range (kg/m^2)	ECOG Performance status (0/1/2/3)	Smoking	Surgical approach (open/laparoscopic)	Median follow-up, range (months)
Xylinas	69.6, 54-76	441/225	28.2, 24-32 (IQR)	445/221(1-3)	NA	519/147	45.5, 24-67 (IQR)
Ito	NA	47/23	NA	NA	NA	49/21	29.2, 1-157
Raman	70, 27-96	257/157	NA	82/165/159/8	NA	NA	16, 2-120
Morizane	74, 38-95	234/111	22.1, 13-34.2	241/103(1-3)	175	244/101	39.9, 6.1-160
Yeh	67, 24-95	204/268	NA	NA	99	269/203	33, 1-233
Huang	68.6, 23.6-91.6	103/95	NA	NA	26	NA	29.1, 6.4-164.9
Xing	NA	78/114	NA	NA	NA	84/145	65, 3-144
Yu	72, 65-76 (IQR)	165/401	NA	399/148/20/1	NA	142/424	31.1, 16.2-55.7
Koguchi	69, 62-75 (IQR)	313/120	NA	NA	138	243/190	35.4, 13.8-74.5 (IQR)
Freifeld	70 (mean)	152/93	29 (mean)	126/98(1-3)	NA	NA	27
Jan	70, 29-96	189/235	NA	NA	49	NA	35, 14-60 (IQR)
Kuroda	71, 38-90	138/49	NA	NA	NA	104/83	49.2, 3.4-209.2
Momota	NA	309/147	NA	446(0-1)/10(2-3)	NA	377/79	40

BMI: body mass index, ECOG: Eastern Cooperative Oncology Group, IQR: interquartile range, NA: not available.

Table 3. Tumor characteristics of the eligible studies

Study	History of bladder cancer	Hydronephrosis	Tumor size	Tumor location (pelvis/ureter)	Tumor multifocality	Adjuvant chemotherapy
Xylinas	244	NA	NA	420/246	164	62
Ito	17	26	NA	0/70	7	23
Raman	NA	NA	NA	NA	NA	55
Morizane	36	201	NA	140/205	51	NA
Yeh	NA	NA	NA	189/193	90	87
Huang	49	NA	NA	NA	NA	21
Xing	NA	119	NA	102/90	52	NA
Yu	111	249	NA	258/308	49	205
Koguchi	NA	NA	NA	239/194	NA	99
Freifeld	80	71	3.4 (mean)	116/85	35	NA
Jan	127	344	NA	191/138	116	40
Kuroda	47	112	NA	NA	NA	NA
Momota	NA	288	NA	175/254	NA	64

NA: not available.

Table 4. Pathologic characteristics of the eligible studies

Study	Tumor grade (low/high)	Pathologic T stage (pT0/is/a/1/2/3/4)	Pathologic N stage (pNx/-/+)	Variant Form	LVI	Concomitant CIS	Positive surgical margin
Xylinas	121/533	326(≤T1)/118/182/40	291/291/84	NA	171	229	NA
Ito	NA	NA	NA	NA	NA	NA	NA
Raman	116/298	3/16/106/60/60/143/26	165/203/46	NA	NA	NA	25
Morizane	222/109	188(≤T2)/152(≥T3)	205/119/21	29	102	43	22
Yeh	112/360	0/60(Tis/a)/130/112/142/28	261/170/41	8	NA	NA	NA
Huang	11/147	198(T3)	198(N0)	NA	31	20	5
Xing	170/22	30(Ta)/162(T1)	192(N0)	NA	NA	NA	NA
Yu	182/388	0/84(Tis/a)/128/134/200/20	NA	NA	119	54	NA
Koguchi	300/127	0/18/66/91/81/153/24	181/221/31	NA	151	NA	30
Freifeld	NA	NA	NA	NA	NA	NA	NA
Jan	22/402	0/0/161(Ta/1)/83/180(T3/4)	399(Nx/-)/25	NA	115	NA	NA
Kuroda	55/132	96(≤T2)/91(≥T3)	0/172/15	NA	65	22	21
Momota	24/432	260(≤T2)/196(≥T3)	431(Nx/-)/25	NA	160	NA	15

LVI: lymphovascular invasion, CIS: carcinoma in situ, NA: not available.

Table 5. Estimation of the hazard ratios

Study	Survival analysis	Threshold of eGFR (ml/min/1.73m^2)	Co-factors	Analysis results
Xylinas	OS	60	Standard clinic-pathological features	Not significant
Ito	PFS	60	cT stage (T3), length of cancer (3cm), maximal diameter of cancer (1.6cm), NLR (3)	Significant
Raman	CSS	60	Gender, race, age (70 yr), ECOG performance status(0,1/2,3), pT stage (T3/T4), LN status, surgical margin status, adjuvant chemotherapy	Not significant
Morizane	CSS	50	ECOG performance status(0/≥1), number of tumor (1/>1), CRP (0.5)	Significant
Yeh	CSS/OS	60	Gender, age (67 yr), smoking, surgery method (laparoscopic/open), tumor location, pT stage, pN stage, tumor grade, adjuvant chemotherapy, hematuria, hydronephrosis and flank pain	Significant/Significant
Huang	PFS/CSS/OS	60	Gender, age (68.6 yr), current smoking, ASA score, recurrent bladder tumor, recurrent contralateral UTUC, tumor grade, LVI, CIS, surgical margin status, adjuvant radiotherapy, adjuvant chemotherapy	Significant/Significant/Significant
Xing	CSS	30	ABCC6 methylation, GDF15 methylation, tumor multifocality, surgery method (laparoscopic/open)	Significant
Yu	PFS	60	BMI, pT stage (≤T2/≥T3), tumor grade, LVI	Significant
	CSS	60	DM, pT stage (≤T2/≥T3), tumor grade, LVI, adjuvant chemotherapy	Significant
	OS	60	Age, BMI, ECOG performance status(0,1/2,3), tumor size, tumor multifocality, pT stage (≤T2/≥T3), tumor grade, LVI, adjuvant chemotherapy	Significant
Koguchi	PFS/OS	60	Change rate of eGFR, age, gender, tumor location, tumor grade, pT stage, pN stage, LVI, surgical margin status	Not significant/Not significant
Freifeld	PFS	50	Age (66 yr), ECOG performance status(0/≥1), hemoglobin, hydronephrosis, pT stage (≤T2/≥T3), tumor architecture	Not significant
Jan	PFS/CSS/OS	60	Gender, blood type, age (69 yr), smoking, hemodialysis, DM or hypertension, previous or concomitant bladder cancer, hydronephrosis, hematuria, pT state, pN stage, tumor grade, LVI. Tumor location, tumor multifocality, tumor size (3cm), tumor architecture, tumor necrosis, adjuvant chemotherapy, NLR (4), PLR (150), MLR (0.4), SII (580)	Not significant/Not significant/Not significant
Kuroda	PFS	60	Tumor histology, pT stage (≤T2/≥T3), tumor grade, pN stage, surgical margin status, LVI, CAR (0.079, NLR (2.035), PLR (165), GPS (1), fibrinogen (337)	Significant
	CSS	60	Urine cytology, tumor histology, pT stage (≤T2/≥T3), tumor grade, pN stage, surgical margin status, LVI, CAR (0.079, NLR (2.035), PLR (165), GPS (1), fibrinogen (337)	Significant
Momota	PFS/CSS/OS	60	age, gender, ECOG performance status, hypertension, CVD, DM, neoadjuvant chemotherapy, hydronephrosis,	Significant/Not significant/Not significant

	tumour location, tumor grade, pT stage (≤T2/≥T3), pN stage, LVI.

eGFR: estimated glomerular filtration rate, OS: overall survival, PFS: progression-free survival, NLR: neutrophil-to-lymphocyte ratio, CSS: cancer-specific survival, ECOG: Eastern Cooperative Oncology Group, LN: lymph node, CRP: C-reactive protein, ASA: American Society of Anesthesiologists, UTUC: upper tract urothelial carcinoma, LVI: lymphovascular invasion, CIS: carcinoma in situ, BMI: body mass index, DM: diabetes mellitus., PLR: platelet-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio, SII: systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, GPS: Glasgow prognostic score: CVD: cardiovascular disease.

Table6. Assessment of quality of the non-randomized controlled trial (RCT) studies using the Newcastle-Ottawa scale for cohort studies.

Study	Selection				Comparability	Outcome			
	REC	SNEC	AE	DOI	CCB	AO	FLO	AFC	Score
Xylinas	★	★	★		★	★	★	★	7
Ito	★	★	★		★	★	★	★	7
Raman	★	★	★		★	★	★	★	7
Morizane	★	★	★		★	★	★	★	7
Yeh	★	★	★		★	★	★	★	7
Huang	★	★	★		★	★	★	★	7
Xing	★	★	★		★	★	★	★	7
Yu	★	★	★		★	★	★	★	7
Koguchi	★	★	★		★	★	★	★	7
Freifeld	★	★	★		★	★	★	★	7
Jan	★	★	★		★	★	★	★	7
Kuroda	★	★	★		★	★	★	★	7
Momota	★	★	★		★	★	★	★	7

REC: Representativeness of the exposed cohort; SNEC: Selection of the non exposed cohort; AE: Ascertainment of exposure; DOI: Demonstration that outcome of interest was not present at start of study; CCB: Comparability of cohorts on the basis of the design or analysis; AO: Assessment of outcome; FLO: Was follow-up long enough for outcomes to occur; AFC: Adequacy of follow up of cohorts

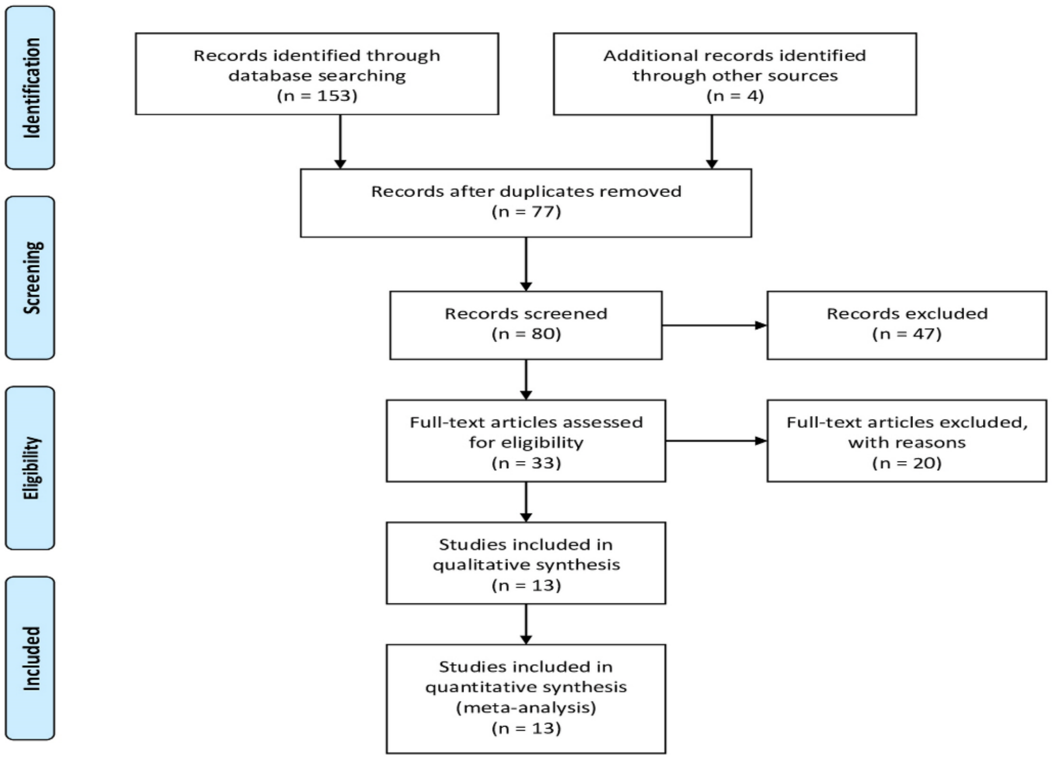


Figure 1. A PRISMA flowchart of the literature search strategy used in our meta-anaysis and systematic review

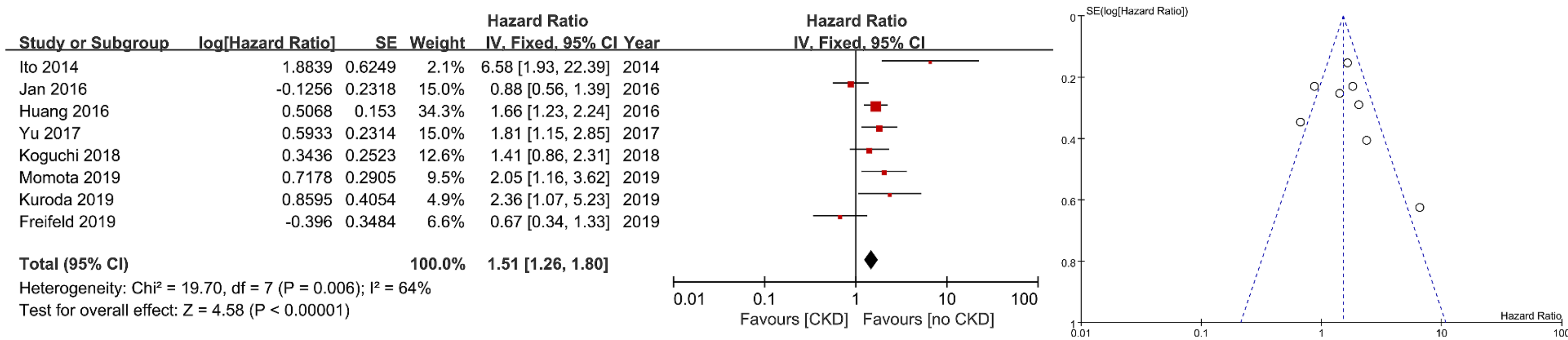


Figure 2. Forest plot and funnel plot of progression-free survival after radical nephronureterectomy according to preoperative renal function, SE: Standard Error, IV: Inverse variance, CI: Confidence Interval, df: degree of freedom

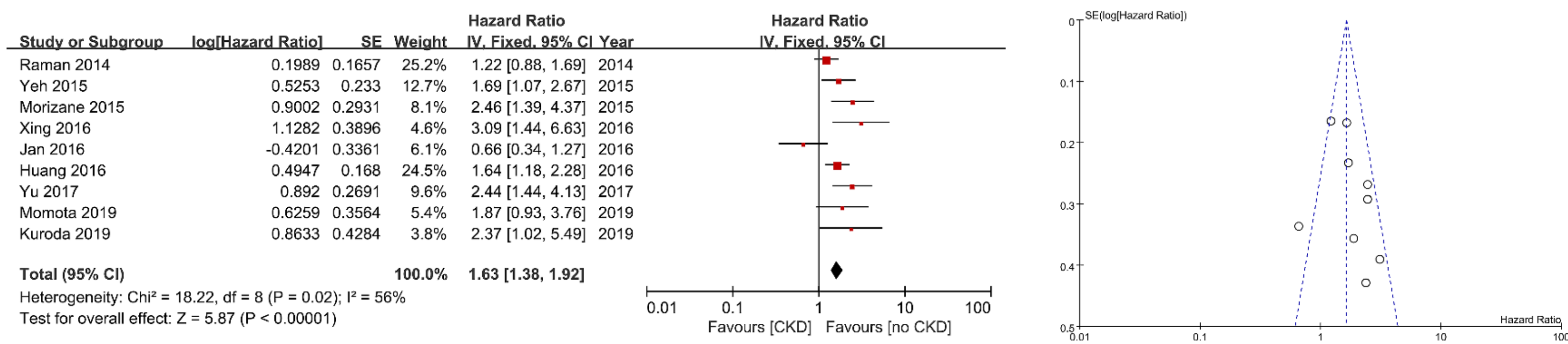


Figure 3. Forest plot and funnel plot of cancer-specific survival after radical nephronureterectomy according to preparative renal function, SE: Standard Error, IV: Inverse variance, CI: Confidence Interval, df: degree of freedom

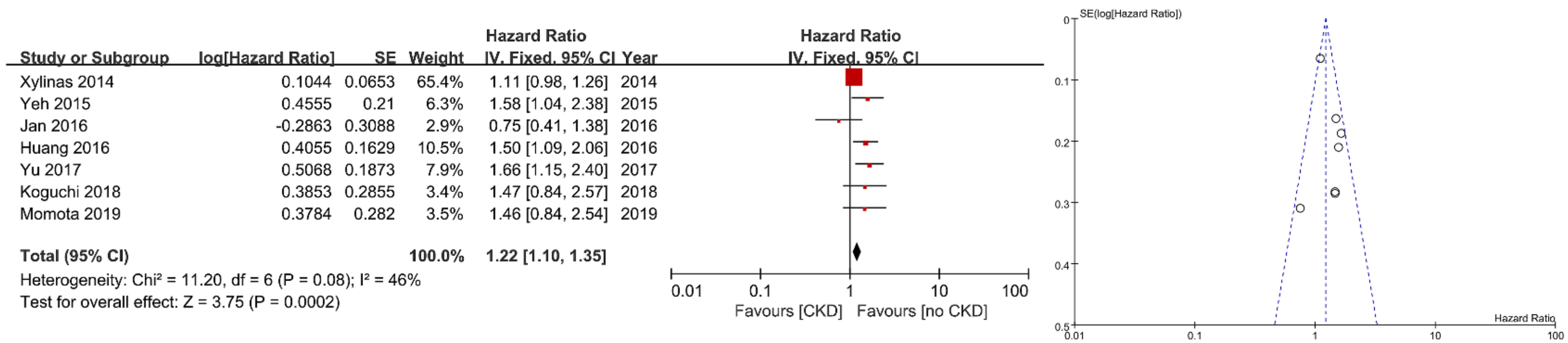
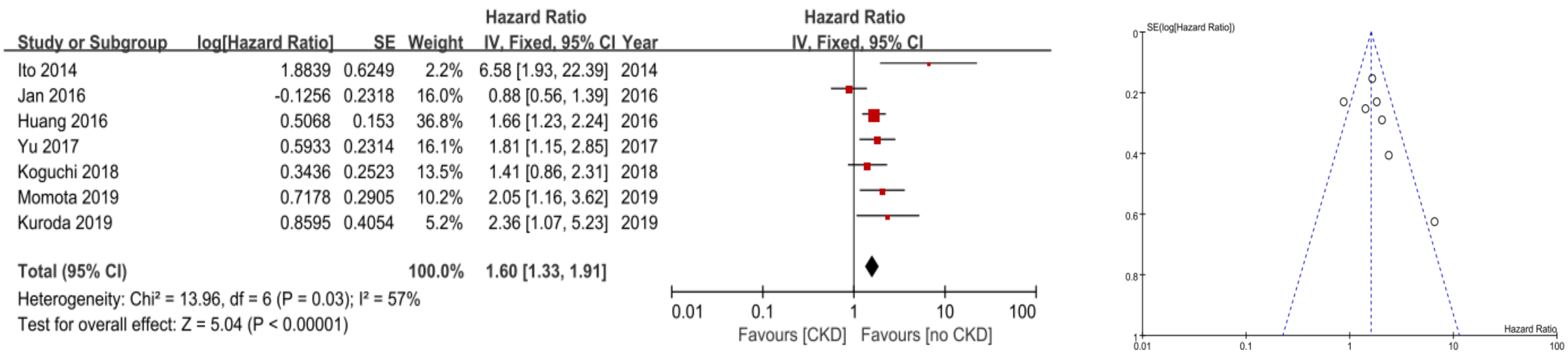
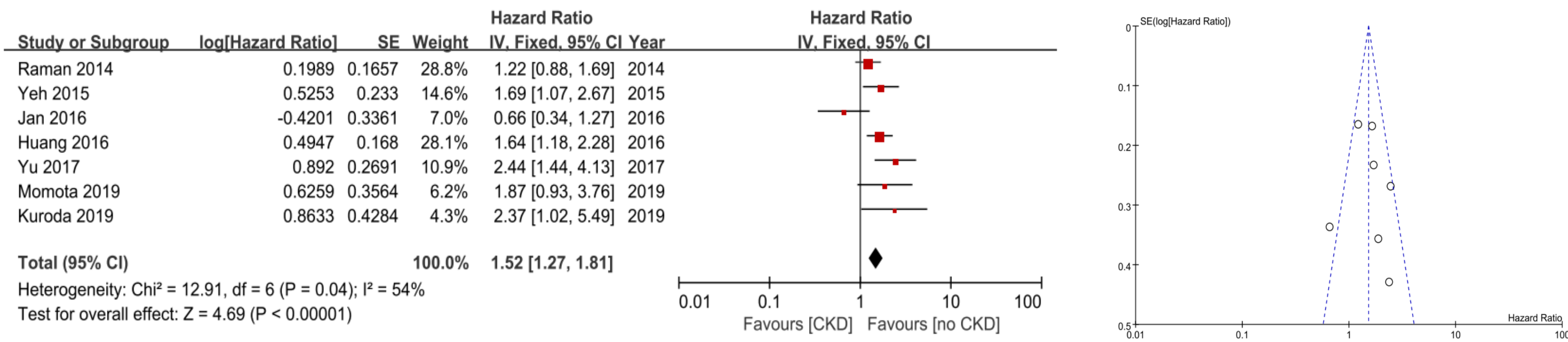


Figure 4. Forest plot and funnel plot of overall survival after radical nephronureterectomy according to preoperative renal function, SE: Standard Error, IV: Inverse variance, CI: Confidence Interval, df: degree of free



Supplementary 1. Forest plot and funnel plot of progression-free survival after radical nephronureterectomy according to preoperative renal function (eGFR 60 ml/min/1.73m²), SE: Standard Error, IV: Inverse variance, CI: Confidence Interval, df: degree of free



Supplementary 2. Forest plot and funnel plot of cancer-specific survival after radical nephronureterectomy according to preoperative renal function (eGFR 60 ml/min/1.73m²), SE: Standard Error, IV: Inverse variance, CI: Confidence Interval, df: degree of free