Kidney-sparing Management Versus Nephroureterectomy for Upper Tract Urothelial Carcinoma: a Systematic Review and Meta-analysis

You Luo*, Dong-Li She*, Hu Xiong*, Sheng-Jun Fu, Li Yang*

Abstract

**Purpose:** To evaluate and update evidence for prognostic effects of kidney-sparing (KS) management and nephroureterectomy (NU) for upper tract urothelial carcinomas. **Materials and Methods:** Pubmed, Embase and the Cochrane Library were retrieved for the identification of comparative studies of kidney-sparing procedure and nephroureterectomy for upper tract urothelial carcinoma prior to December 2014. The data were extracted independently by 2 reviewers and the quality of the included studies was assessed. Review Manager 5.3 and STATA 13 were used to perform the meta-analysis. **Results:** Twenty-three observational studies including 1,587 KS and 3,996 NU were evaluated. The results of the meta-analysis showed that nephroureterectomy had no significant benefit with regard to intravesical recurrence (IRFS), metastasis (MFS), cancer specific survival (CSS) and overall survival (OS) except the total tumor recurrence (RFS) when compared with kidney sparing management. The respectively pooled outcomes were HR 1.36 (0.69-2.68, \(P=0.38\)) for IRFS, 1.09 (0.59-2.01, \(P=0.78\)) for MFS, 1.17 (0.77-1.79, \(P=0.47\)) for CSS, 1.50 (0.90-2.48, \(P=0.12\)) for OS and 1.61 (1.03-2.51, \(P=0.04\)) for RFS. **Conclusions:** On the whole, kidney-sparing management had equivalent prognostic effect on upper tract urothelial carcinoma as the standard nephroureterectomy except in tumor recurrence. However, the results should be interpreted with caution for lack of stage and grade stratification and multi-center randomized controlled trials are still needed to verify our results.

Keywords: Upper tract urothelial carcinoma - kidney-sparing management - nephroureterectomy - meta-analysis

Introduction

Upper tract urothelial carcinoma (UTUC) is rare and occupied 5% of the urothelial carcinoma (Munoz and Ellison, 2000; Siegel et al., 2013). The standard treatment of UTUC is nephroureterectomy (NU) with bladder cuff resection which means one kidney would be lost after this extirpative management. It yields high risk of followed chronic kidney disease and makes following pharmacotherapy treatment restricted because of impaired renal function (Malcolm et al., 2009). Renal function preservation is becoming recognized and kidney-sparing procedures are reserved for selected patients with low-grade UTUC in EAU guidelines (Roupret et al., 2013). Kidney-sparing management (KS) has been reported with durable prognostic outcomes as nephroureterectomy in several studies (Gadzinski et al., 2010; Jeldres et al., 2010; Cutress et al., 2013; Fukushima et al., 2014). Kidney preservation treatments mainly comprise segmental ureterectomy and endoscopic resection or ablation. With the advance of endoscopic techniques, these conservative managements become popular for UTUC treatment.

However, due to low incidence of UTUC, the paucity of comparative data makes the weak evidence of KS. Herein we summarize the published literatures and perform a meta-analysis to update the evidence of oncologic outcomes of kidney-sparing management.

Materials and Methods

Search strategy and literature screening

A literature search of PubMed, Embase, and The Cochrane Library was conducted by two independent investigators (DL She and Y Luo) according to the PICOS principle to retrieve the clinical studies through to December 2014. The search terms used were “ureter cancer”, “renal pelvis cancer”, “upper tract urothelial carcinoma”, “nephroureterectomy”, “ureterectomy”, “nephron sparing”, “survival”, “hazard ratio” and “mortality”, etc. References in the retrieved literature and previous systematic reviews were also identified for any relevant studies. The eligibility criteria were that any comparative studies simultaneously included both nephroureterectomy and nephron-sparing management.
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for upper tract urothelial carcinoma. Any study containing
any following criteria was excluded: (1) any study
labeled conservative management but actually containing
nephrectomy compared with nephroureterectomy; (2)
no related data could be extracted or calculated; or
(3) duplicate published papers or studies containing
overlapping patients. This systematic review was
performed in compliance with the Preferred Reporting
Items for Systematic Reviews and Meta-Analyses
statement (PRISMA) (Moher et al., 2009).

Quality assessment and data extraction

The quality of the included studies was independently
assessed by 2 investigators (Y Luo and DL She) using
the Oxford Centre for Evidence-based Medicine Levels
of Evidence (March 2009) (OCEBM 2009) (Phillips et
al., 2009) and the data extraction was also performed
and cross-checked. If there was a discrepancy of opinions or
results, it was solved by group discussion. We extracted
the name of the first author, year of publication, regions or
data sources, number of analyzed patients, age, approaches
to kidney-sparing management, cancer category, reported
results, follow-up years from the citations. The data were
extracted from the reported original data, if possible.
When no direct survival data were included, it can be
calculated or estimated by using the methods that Tierney
et al provided (Tierney et al., 2007), or obtained from
related systematic review including this study. Contacting
responding author was another action for the original
data. Studies were excluded if above methods were failure.
pooled results showed kidney-sparing management yielded significantly higher risk of tumor recurrence than nephroureterectomy. However, no significant differences were observed in the intravesical recurrence, recurrence hazard ratios of kidney sparing management versus nephroureterectomy were 1.07 (0.75-1.52, \( P=0.70 \)) and 1.36 (0.69-2.68, \( P=0.38 \)) in univariate and multivariate groups, respectively (Figure 3).

Figure 3. Forest Plot of Recurrence Free Survival (RFS) Hazard Ratio

Figure 4. Forest Plot of Metastasis Free Survival (MFS) Hazard Ratio

Table 1. Characteristics of Included Studies Compared KS and NU

<table>
<thead>
<tr>
<th>Studies</th>
<th>Regions</th>
<th>Duration</th>
<th>n (KS/NU)</th>
<th>Age (range) years</th>
<th>KS approaches</th>
<th>Cancer</th>
<th>Outcomes</th>
<th>Follow-up (range) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall 1998</td>
<td>USA</td>
<td>1960.1-1992.12</td>
<td>42/194</td>
<td>(30-95)</td>
<td>DU, SU, open-excision, ablation</td>
<td>UTUC (G1, G2, G3)</td>
<td>RFS CSS</td>
<td>Md64 (1-255)</td>
</tr>
<tr>
<td>Shiraishi</td>
<td>Japan</td>
<td>1995-2001</td>
<td>9/10</td>
<td>Mn69.7</td>
<td></td>
<td>UTUC (G1, G2, G3)</td>
<td>RFS</td>
<td>NA</td>
</tr>
<tr>
<td>Chen 2005</td>
<td>Taiwan</td>
<td>1993.1-2003.12</td>
<td>16/78</td>
<td>Mn70.5 (38-91)</td>
<td>SU, ureteroscopy management</td>
<td>Uretrect cancer (G1, G2, G3)</td>
<td>RFS CSS</td>
<td>Mn49.3 (1-136)</td>
</tr>
<tr>
<td>Roupret</td>
<td>France</td>
<td>1990-2004</td>
<td>43/54</td>
<td>Mn68</td>
<td>PNR, ureteroscopic resection</td>
<td>UTUC (low, high grade)</td>
<td>CSS</td>
<td>Mn54</td>
</tr>
<tr>
<td>Lehmann</td>
<td>Germany</td>
<td>1975-2004</td>
<td>51/91</td>
<td>Md68 (29-85)</td>
<td>PU</td>
<td>Uretrect cancer (G1, G2, G3)</td>
<td>CSS</td>
<td>Md96</td>
</tr>
<tr>
<td>Giannarini</td>
<td>Switzerland</td>
<td>1974.12-2004.12</td>
<td>19/24</td>
<td>Md72 (31-86)</td>
<td>PU</td>
<td>Distal ureter cancer (G1, G2, G3)</td>
<td>CSS OS</td>
<td>Md58 (3-260)</td>
</tr>
<tr>
<td>Lucas</td>
<td>USA</td>
<td>1990-2005</td>
<td>39/77</td>
<td>(33-89)</td>
<td>PNR</td>
<td>UTUC (low, high grade)</td>
<td>CSS OS</td>
<td>Md45.8 (0.5-129)</td>
</tr>
<tr>
<td>Dragicicic</td>
<td>Serbia</td>
<td>1998.1-2002.12</td>
<td>21/86</td>
<td>Md67 (38-86)</td>
<td>PU, ablation</td>
<td>UTUC (G1, G2, G3)</td>
<td>OS</td>
<td>Md67 (46-88)</td>
</tr>
<tr>
<td>Gadzinski</td>
<td>USA</td>
<td>1996-2004</td>
<td>34/62</td>
<td>Mn70 (33.5-93.2)</td>
<td>Endoscopic management</td>
<td>UTUC (low, high grade)</td>
<td>IRFS MFS CSS OS</td>
<td>Md56.6 (2.3-146.7)</td>
</tr>
<tr>
<td>Jeldres</td>
<td>USA</td>
<td>(SEER) 1988-2006</td>
<td>569/1222</td>
<td>Mn72 (30-95)</td>
<td>SU</td>
<td>Uretrect cancer (G1, G2, G3, G4)</td>
<td>CSS</td>
<td>Md30</td>
</tr>
<tr>
<td>Raymundo</td>
<td>USA</td>
<td>1991-2009.10</td>
<td>21/99</td>
<td>Mn72.2 (37-98)</td>
<td>Percutaneous/ureteroscopic resection/fulguration, basketing of UT-UC</td>
<td>UTUC (G1, G2, G3)</td>
<td>RFS IRFS MFS</td>
<td>Mn17.9 (13.2-24.6)</td>
</tr>
<tr>
<td>Shi 2012</td>
<td>China</td>
<td>1997.4-2008.4</td>
<td>75/64</td>
<td>Mn66.6 (30-85)</td>
<td>SU, endourologic management</td>
<td>UTUC (well, moderate, poor differentiation)</td>
<td>OS</td>
<td>Md43.4 (0.2-120)</td>
</tr>
<tr>
<td>Grasso</td>
<td>USA</td>
<td>1996.1-2011.8</td>
<td>80/80</td>
<td>Md73 (45-93)</td>
<td>Ureteroscopy management</td>
<td>UTUC (low, high grade)</td>
<td>MFS CSS OS</td>
<td>Mn38.2 (1-185.3)</td>
</tr>
</tbody>
</table>
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Table 1 (continued). Characteristics of Included Studies Compared KS and NU

<table>
<thead>
<tr>
<th>Studies</th>
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<th>n (KS/ NU)</th>
<th>Age (range) years</th>
<th>KS approaches</th>
<th>Cancer</th>
<th>Outcomes</th>
<th>Follow-up (range) months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colin 2012</td>
<td>France</td>
<td>1995.1-2009.12</td>
<td>52/416</td>
<td>Md70.1/69.1</td>
<td>SU</td>
<td>UTUC (G1, G2, G3)</td>
<td>RFS CSS</td>
<td>Md26 (IQR10-48)</td>
</tr>
<tr>
<td>Bin 2012</td>
<td>USA</td>
<td>2000.10-2010.12</td>
<td>27/33</td>
<td>Md73 (IQR64-82.8)</td>
<td>PU, endoscopic resection</td>
<td>Ureter cancer (low, high grade)</td>
<td>RFS CSS</td>
<td>Md29 (IQR11.8-44.4)</td>
</tr>
<tr>
<td>Bagrodia 2013</td>
<td>USA</td>
<td>1992-2006</td>
<td>81/754</td>
<td>Md69 (32-97)</td>
<td>PU</td>
<td>UTUC (low, high grade)</td>
<td>RFS CSS</td>
<td>Md34 (1-246)</td>
</tr>
<tr>
<td>Cutress 2013</td>
<td>UK</td>
<td>1991.1-2011.9</td>
<td>59/70</td>
<td>Md74.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fajkovic 2013</td>
<td>Austria</td>
<td>1996-2012</td>
<td>20/178</td>
<td>Mn69.2</td>
<td>Endoscopic management</td>
<td>UTUC (low, high grade)</td>
<td>CSS OS</td>
<td>Mn20.4</td>
</tr>
<tr>
<td>Klatte 2013</td>
<td>Europe multicenter</td>
<td>NA</td>
<td>177/177</td>
<td>NA</td>
<td>SU</td>
<td>Ureter cancer</td>
<td>CSS</td>
<td>Md35</td>
</tr>
<tr>
<td>Hung 2014</td>
<td>Taiwan</td>
<td>2004.7-2010.8</td>
<td>35/77</td>
<td>Md68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoffman 2014</td>
<td>Israel</td>
<td>2000-2010</td>
<td>25/22</td>
<td>Md64/76</td>
<td>Endoscopic resection</td>
<td>UTUC (low, high grade)</td>
<td>IRFS CSS</td>
<td>Md26/57</td>
</tr>
<tr>
<td>Fukushima 2014</td>
<td>Japan</td>
<td>1977-NA</td>
<td>43/86</td>
<td>NA</td>
<td>Distal ureterectomy</td>
<td>Distal ureter cancer (G1, G2, G3)</td>
<td>IRFS CSS</td>
<td>Md50 (16-103)</td>
</tr>
<tr>
<td>Dalpiaz 2014</td>
<td>Austria</td>
<td>1984.1-2011.3</td>
<td>49/42</td>
<td>Md71.5/70.3</td>
<td>Distal ureterectomy</td>
<td>Distal ureter cancer (G1, G2, G3)</td>
<td>IRFS CSS OS</td>
<td>Msd1.51/51.5 (4-290)</td>
</tr>
</tbody>
</table>

*SEER=Surveillance, Epidemiology and End Results database; KS=kidney sparing; SU=segmental ureterectomy; PU=partial ureterectomy; DU=distal ureterectomy; PNR=percutaneous nephroscopic resection; Mn=mean; Md=median; UTUC=upper tract urothelial carcinoma; IQR=interquartile range; NA=not applicable

Table 5.

Figure 5. Forest Plot of Cancer Specific Survival (CSS) Hazard Ratio

Figure 6. Forest Plot of Overall Survival (OS) Hazard Ratio

of 1.09 (0.59-2.01, P=0.78) did not validate this result, temporarily (Figure 4). Univariate cancer specific survival was acquired from 11 studies and multivariate outcomes were from 8 studies. Both of pooled outcomes revealed equivalent cancer mortality risk based on the hazard ratio of 0.89 (0.74-1.07, P=0.21) in univariate CSS and 1.17 (0.77-1.79, P=0.47) in multivariate CSS (Figure 5). Additionally, no significant overall survival differences were observed from the pooled OS outcomes in univariate hazard of 1.14 (0.83-1.57, P=0.41) and multivariate hazard of 1.50 (0.90-2.48, P=0.12) (Figure 6).

Publication bias and sensitive analysis

To assure compliance with Cochrane handbook recommendations, Egger’s test for funnel plot asymmetry was conducted in meta-analysis included at least ten studies as a rule of thumb (Higgins and Green, 2011). Hence, we performed this test in CSS meta-analysis. The P value of Egger’s test in the univariate CSS, multivariate CSS group were 0.158 and 0.298, respectively. No significant evidence of publication bias was observed.
We performed leave-one-out sensitive analysis to detect any single study affected systematic result and effect models alteration to check the feasibility of the pooled result. No pooled result was altered using sensitive analysis (results were omitted) except RFS and univariate MFS which were “marginal significant”. It showed that the conclusion kidney-sparing management had more tumor recurrence risk than nephroureterectomy was not feasible and could easily be altered by following few studies. Therefore, more studies were needed to validate the recurrence risk between kidney-sparing management and nephroureterectomy.

Discussion

Our meta-analysis enrolled twenty-three studies that contained various oncologic outcomes and majority of the pooled results favored kidney sparing management as an alteration for upper tract urothelial carcinoma with equivalent survival outcomes as nephroureterectomy. However, this was based on low level of evidences and no stage or grade stratification was conducted. Many factors affected the survival to different extent. Seisen et al (Seisen et al., 2014) summarized clinicopathologic factors on intravesical recurrence after nephroureterectomy in upper tract urothelial carcinoma. Of the results gender, prior bladder cancer, patient with chronic kidney disease were the risk factors, and tumor related factors such as positive cytology, tumor location, multifocality, invasive pT stage, and necrosis were significant recurrence predictors. Additionally, laparoscopic nephroureterectomy, extravesical bladder cuff resection and positive surgical margin were also the predictors. Previous ureteroscopy seemed to be an independent intravesical recurrence risk factor (Luo et al., 2013), but it’s still controversial (Ishikawa et al., 2010; Gurbuz et al., 2011; Nison et al., 2013). Tumor grade was another impact factor of oncologic outcome. Cutress et al (Cutress et al., 2013) found that compared with nephroureterectomy, kidney preservation treatment had significantly lower survival rate of IRFS, PFS, CSS and OS in G2 and G3 but equivalent in G1. On the other hand, grade 2 and grade 3 upper tract urothelial carcinoma was significantly poor compared with grade 1 (Grasso et al., 2012).

As a compromise, initial conservative management with regular surveillance and followed extirpative procedure for disease advance could be a sufficient solution. Recent reports suggest that delayed nephroureterectomy do not affect the oncologic survival significantly (Boorjian et al., 2005; Gadzinski et al., 2012; Sundi et al., 2012). Initial ureteroscopic ablation didn’t affect the recurrence and cancer specific mortality after radical nephroureterectomy with the hazard ratio of 0.79, \( P = 0.185 \) and 0.7, \( P = 0.078 \), respectively (Gurbuz et al., 2011). Yakoubi et al summarized previously published comparative reports of endoscopic procedure and nephroureterectomy and preliminarily concluded equivalent overall and cancer specific survival based on the low level of evidences (Yakoubi et al., 2014). Our meta-analysis was compliance with these results. It’s safe to apply endoscopic procedures for initial management of upper tract urothelial carcinoma. However, up-stage and progression as a result of delayed extirpative treatment may damage the following nephroureterectomy (Waldert et al., 2010).

Though above results showed no significant survival advantage using nephroureterectomy versus using kidney preservation treatment. It cannot compellingly conclude that kidney preservation procedure provided equivalent tumor control in all upper tract urothelial carcinoma patients. Because this equivalent effect probably was contributed by low grade or low stage upper tract urothelial carcinoma, paucity of the number, low quality of included studies and selection bias (though multivariate analysis was conducted). Our results merely provided a comprehensive outcome and should be interpreted with caution. No more detail information such as grade or stage stratification that could give a direct guidance for clinical practice was provided. Hence, kidney preservation management may be only conservatively applied in low-grade upper tract urothelial carcinoma for now. Additionally, considering the low incidence rate of upper tract urothelial carcinoma, multi-institute randomized controlled trials are needed for further verification.

In conclusion, kidney-sparing management had equivalent prognostic effect on upper tract urothelial carcinoma as the standard nephroureterectomy except in tumor recurrence, overall. But the results should be interpreted with cautious for lack of stage and grade stratification and multi-center randomized controlled trials are still needed to further verify our results.

References


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