Surgical management for upper urinary tract transitional cell carcinoma

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TABLE OF CONTENTS

[Intervention Review]

Surgical management for upper urinary tract transitional cell carcinoma

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ABSTRACT

Background

Upper tract transitional cell carcinomas (TCC) are uncommon and aggressive tumours. There are a number of surgical approaches to manage this condition including open radical nephroureterectomy and laparoscopic procedures.

Objectives

To determine the best surgical management option for upper tract transitional cell carcinoma.

Search methods

A sensitive search strategy was developed to identify relevant studies for inclusion in this review. The following databases were searched for randomised trials evaluating surgical approaches to the management of upper tract TCC: Medline EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, British Nursing Index, AMED, LILACS, Web of Science®, Scopus, Biosis, TRIP, Biomed Central, Dissertation Abstracts, and ISI Proceedings.

Selection criteria

The following criteria that were considered for this review.

Types of studies - All randomised or quasi-randomised controlled trials comparing the various surgical methods and approaches for the management of localised upper tract transitional cell carcinoma.

Types of participants - All adult patients with localised transitional cell carcinoma. Localised disease was defined as limited to the kidney or ureter with no gross regional lymph nodal enlargement on imaging.

Types of interventions - Any surgical method or approach for managing localised upper tract transitional cell carcinoma.

Types of outcome measures - Overall and cancer-specific survival were primary outcomes. Surgery-related morbidity. Quality of life and health economics outcomes were secondary outcomes.

Data collection and analysis

Two review authors examined the search results independently to identify trials for inclusion.

Main results

We identified one randomised controlled trial that met our inclusion criteria. The trial showed that the laparoscopic approach had superior peri-operative outcomes compared to open approach. Laparoscopic was superior and statistically significant for blood loss (104 mL (millilitres) versus 430 mL, P < 0.001) and mean time to discharge (2.3 days versus 3.7, P < 0.001). Oncological outcomes (bladder tumour-free survival, metastasis-free survival, cancer-specific survival curves), at a median follow up of 44 months and in organ-confined disease, were comparable for both groups.

Authors' conclusions

There is no high quality evidence available from adequately controlled trials to determine the best surgical management of upper tract transitional cell carcinoma. However, one small randomised trial and observational data suggests that laparoscopic approach is associated with less blood loss and early recovery from surgery with similar cancer outcomes when compared to open approach.

PLAIN LANGUAGE SUMMARY

Surgery for upper tract transitional cell carcinoma

Upper tract transitional cell carcinoma is an uncommon cancer mainly affecting the draining system of the kidney (kidney pelvis) and ureter (the tube through which urine passes from the kidney to the bladder). The main treatment approach for this condition is surgical removal of the malignant area. There are a number of surgical techniques for this procedure and the aim of this review was to compare them and determine which was the most effective in terms of surgical ease, patient morbidity, clinical outcome and cost. Our search of the literature found no high quality evidence comparing different surgical techniques. Evidence from one small randomised trial and observational studies suggests that laparoscopic surgical intervention may reduce blood loss, post-operative pain and hospital stay. However, the quality of the evidence is poor and, therefore, it is not possible to recommend the most effective surgical procedure to replace the existing clinical practice for managing upper tract transitional cell carcinoma.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

We performed a comprehensive search for randomised or quasi-randomised controlled trials that compared the pre-stated objectives. Only one randomised control trial comparing laparoscopic nephroureterectomy with open nephroureterectomy was identified (Simone 2009).This trial showed that the laparoscopic approach had superior peri-operative outcomes when compared with the open approach, which were statistically significant for blood loss (104 mL versus 430 mL; P <0.001) and mean time to discharge (2.3 days versus 3.65 days). The oncological outcome (bladder tumour free survival, metastasis free survival, cancer-specific survival curves) at a median follow-up of 44 months, in organ confined disease, were comparable for the two groups

There were 22 comparative studies comparing various options of radical nephroureterectomy (open, laparoscopic) as shown in Table 4. Whilst they all showed better early surgical outcomes in the laparoscopic group and comparable oncological outcomes, they were however excluded as they were all retrospective studies. Our search revealed 5 retrospective studies comparing various techniques (open, transurethral and laparoscopic) of dealing with distal end of the ureter. We found three comparative studies between nephron sparing surgery and nephroureterectomy and just one study comparing percutaneous management and nephroureterectomy. These comparisons were again retrospective and were therefore excluded from the study

BACKGROUND

Upper tract transitional cell carcinomas (TCC) are uncommon and aggressive tumours. There are a number of surgical approaches to manage this condition including open radical nephroureterectomy and laparoscopic procedures.

Description of the condition

Upper tract transitional cell carcinoma (TCC) arises from the renal pelvis, calyces and ureters. These tumours are uncommon and constitute only 5% of the TCCs of the entire renal tract (Campbell-Walsh 2003). TCCs of the renal pelvis account for 10% of all renal tumours and ureteric TCCs are even less common (Jabbour 2000). Bilateral disease is extremely rare and occurs in 2% to 4% of the cases (Browne 2005). Although histologically similar to bladder TCCs, upper tract transitional cell carcinoma is a more aggressive tumour with a tendency to multifocality, local recurrence and progression to an advanced stage (Browne 2005; David 2002; Muntener 2007).

The risk of upper tract TCCs increases with age and commonly occurs between the sixth and seventh decade of life. Men have a two to three times more risk of developing upper tract TCCs as compared to women (Campbell-Walsh 2003; David 2002). Cigarette smoking is the most significant acquired risk factor for upper-tract TCCs (Jensen 1988; McLaughlin 1992). Balkan endemic nephropathy (Petkovic 1975) (chronic tubulo-interstitial nephritis), analgesic abuse (particularly phenacetin), exposure to chemicals (e.g. aniline dye, coal, coke, tar, asphalt), chronic bacterial infection, and chemotherapy drugs (e.g., cyclophosphamide and ifosfamide), have all been implicated (Jensen 1988; McCredie 1982).

Upper tract transitional cell carcinoma is rarely asymptomatic. Frank or microscopic haematuria is the most common presentation followed by loin pain (Campbell-Walsh 2003). Other clinical presentations include renal colic, palpable mass, weight loss, anorexia, and bone pain. Diagnosis is based on clinical, cytological, endoscopic and imaging grounds (Johnson 2005; Painter 2007). Useful imaging modalities include retrograde pyelography, renal ultrasound, computerised tomography (CT) and magnetic resonance (MR) urography (Browne 2005). Stage and grade at presentation dictate prognosis, with staging being the single most important prognostic indicator (Olgac 2004).

Description of the intervention

Open nephroureterectomy (ONU) has been the standard surgical option for upper tract TCCs, with a normally functioning contra-lateral collecting system. The procedure consists of total nephroureterectomy, with excision of the bladder cuff around the ureteric orifices to prevent tumour recurrence in the ureteric stump or around the ipsilateral ureteric orifice. The procedure entails either two incisions or a single long incision for adequate exposure. As a result there is significant morbidity in the form post-operative pain and therefore prolonged hospitalisation (Rassweiler 2004). There has been considerable advancement in recent years, with the aim of reducing post-operative pain and hospital stay, in minimal invasive surgery. Some of the viable alternates include laparoscopic nephroureterectomy (LNU), ureteroscopic resection/fulguration, or percutaneous management.

Reports have proven that LNU has significantly reduced morbidity compared to ONU, although long term oncological efficacy of LNU and ONU are similar (Arancibia 2007; Bariol 2004; Busby 2007; David 2002; Muntener 2007; Rassweiler 2004). For these reasons LNU is steadily becoming the standard procedure of choice for upper tract TCCs in various centres, and especially for bulky tumours.

With the recent development of sophisticated ureteroscopes, endoscopic management of low-grade lesions measuring < 1.5 cm (centimetres) with normal contralateral kidneys has been reported in various studies to be a very favourable option (David 2002; Johnson 2005;Mugiya 2006; Soderdahl 2005).

However, the need for long-term surveillance and patient suitability are limiting factors. Laser therapy and electro-cautery are commonly used in these settings. Adjuvant topical therapy (mitomycin) has been suggested to reduce recurrence of disease following endoscopic therapy (Keeley 1997).

In some reports, the percutaneous approach combined with resection of the tumours has been suggested to be a useful option for low-grade, large tumours (Jabbour 2000; Soderdahl 2005). For patients with solitary, bilateral tumours, severe renal insufficiency, and severe co-morbidities, there are three surgical options: partial nephrectomy; segmental ureteric resection with re-anastomosis; or ureteroscopic management (Campbell-Walsh 2003; Johnson 2005).

Furthermore, there are various techniques to deal with the lower end of the ureter during nephroureterectomy, such as open excision, laparoscopic or endoscopic-assisted methods (Ko 2007; Matin 2005; Romero 2007; Salvador-Bayarri 2002; Walton 2009). However, there is no consensus on the best way to deal with it, and surgical practice remains hostage to surgeons' preferences and training .

How the intervention might work

Surgical excision of upper tract transitional cell carcinoma is considered the standard of care. This can be achieved either by open or by the key-hole approach (laparoscopy). In addition, the removal of the ureter along with a cuff of bladder is considered an essential part of the procedure, and which may need a prior endoscopic incision or a second open surgical incision. There are some reports of pure endoscopic (retrograde or percutaneous) control of low-grade upper tract transitional cell carcinoma in a selected population (Lee 1999).

Why it is important to do this review

Upper tract transitional cell carcinoma, although relatively rare as compared with other urological cancer, has a tendency for multifocality and aggressive behaviour (local recurrences and metastases). The traditional and standard therapeutic approach of open nephroureterectomy has been challenged by various minimally invasive procedures, including laparoscopic surgery. Many techniques are being offered for dealing with this surgically challenging problem, and it is important that an up-to-date appraisal of literature, in the form of a systematic review, be undertaken to inform clinical practice.

OBJECTIVES

To determine the best surgical management of upper tract transitional cell carcinoma.

The following comparisons were pre-stated:

1. whether open radical nephroureterectomy is better than laparoscopic nephroureterectomy;

2. whether nephroureterectomy is better than conservative localised resection of ureter, where indicated;

3. whether open surgical resection (local or nephroureterectomy) is better than endoscopic resection and surveillance, where indicated;

4. whether open surgical method of handling the lower end of the ureter is better than endoscopic or laparoscopic assisted methods.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised or quasi-randomised controlled trials comparing the various surgical methods and approaches for the management of localised upper tract transitional cell carcinoma.

Types of participants

All adult patients with localised transitional cell carcinoma. Localised disease was defined as limited to the kidney or ureter, with no gross lymph nodal enlargement on imaging.

Types of interventions

Any surgical method or approach for managing localised transitional cell carcinoma of the upper urinary tract.

Types of outcome measures

Primary outcomes

Overall and cancer-specific survival following surgical resection of upper tract TCC using different approaches.

Secondary outcomes

Early surgical outcome

Need for re-operation
Operative complications
Post-operative morbidity / mortality
Length of operation
Length of hospital stay
Duration of catheterization
Analgesic requirement
Positive surgical margins (local resection of ureter)

Cancer outcome measures

Incidence of local recurrence or progression
Incidence of distant metastasis

Health-related quality of life (HRQOL) outcome measures

Generic HRQOL measures (e.g. SF-36, Ware 1992)
Disease-specific HRQOLmeasures (e.g.UCLA PCI, Litwin 1998)

Health economic outcome measures

Resource implications of differences in outcomes
Resource implications of differences in impact on HRQOL
Formal economic analysis (cost utility)
Length of hospital stay (days) and associated costs (in GBP)

Search methods for identification of studies

A sensitive search strategy was developed to identify relevant studies for inclusion in this review. Specific search terms were used in conjunction with the Cochrane highly sensitive search strategy for RCTs as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (designed in OVID version of MEDLINE) (Cochrane Handbook 2009). The terms used along with the dates for all the databases are described in 'Appendix 1'.

Data collection and analysis

A single randomised controlled trial was identified during the search strategy. This precludes any formal meta-analysis; hence a narrative approach was adopted to describe the study.

Selection of studies

A list of titles and abstracts of potentially relevant clinical studies were generated by the search strategy and imported in to a bibliographic software (EndNote®). This list was screened by two authors independently (BR and IE) and fully published papers (non abstracts) were retrieved where appropriate. These papers were further assessed to ensure they met the inclusion criteria of this review and data extraction.

Data extraction and management

Data was extracted from each identified paper independently by two reviewers and cross checked. The extracted data included information on trial design, participants, types of interventions, and outcome measures. Data analyses compared radical surgery with other primary surgical modalities and comparisons were made for each of the outcomes. Also, comparisons were made between different surgical approaches

Assessment of risk of bias in included studies

Trial quality was assessed according to the method of randomisation, allocation concealment, adequate descriptions of numbers, and reasons for patient withdrawal, as detailed in the *Cochrane Handbook for Systematic Review of Interventions*.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The results of the search strategies are summarised in 'Table 1'. Of the 400 potentially relevant publications identified and screened for retrieval, just one randomised control trial comparing early surgical and oncological outcomes between laparoscopic nephroureterectomy and open nephroureterectomy was identified. The majority of the remaining studies were excluded, generally due to the lack of suitability of study design or intervention. Of the excluded studies thirty-one (Bariol 2004;

Capitanio 2009; Chung 2007; Chung 2008; Dragicevic 2009; Giannarini 2007; Gill 2000; Goel 2002; Greco 2009; Hattori 2006; Hsueh 2004; Hsueh 2007; Kawauchi 2003; Landman 2002;Li 2001 Manabe 2007; Matsui 2002; Muller 2007; Okeke 2002; Ogegawa 2006; Raman 2006; Rassweiler 2004; Stifelman 2001; Taweemonkongsap 2008; Ko 2007; Matin 2005; Romero 2007; Salvador-Bayarri 2002; Lee 1999; Lucas 2009; Walton 2009) were retrieved for detailed evaluation.

Included studies

Our review identified just one randomised control trial (Simone 2009) comparing laparoscopic nephroureterectomy with open nephroureterectomy that met inclusion criteria. Forty patients with non-metastatic upper tract TCC were randomised to open nephroureterectomy and 40 patients to the laparoscopic approach. Reported outcomes included operation times, the extent of blood loss, hospital stay, bladder tumour-free survival, metastatic-free survival and cancer-specific survival.

Excluded studies

A number of retrospective non-randomised studies making the comparison between the pre-stated objectives ('Table 2') were identified in this study. Observational data from these studies suggested that laparoscopic surgical interventions either complete or in combination with open excision of the lower end, reduced postoperative pain, hospital stay and resumption to normal activities, in comparison to open surgery (Bariol 2004; Capitanio 2009; Chung 2007; Chung 2008; Gill 2000; Goel 2002; Greco 2009; Hattori 2006; Hsueh 2004; Hsueh 2007; Kawauchi 2003; Landman 2002; Li 2001; Manabe 2007; Matsui 2002; Muller 2007; Okeke 2002; Ogegawa 2006; Raman 2006; Rassweiler 2004; Stifelman 2001; Taweemonkongsap 2008).

There were five retrospective studies identified in our search that compared various techniques of en-bloc excision of the lower ureter ('Table 3'). However, none of the studies showed any statistically significant advantage over the other (Ko 2007; Matin 2005; Romero 2007; Salvador-Bayarri 2002; Walton 2009).

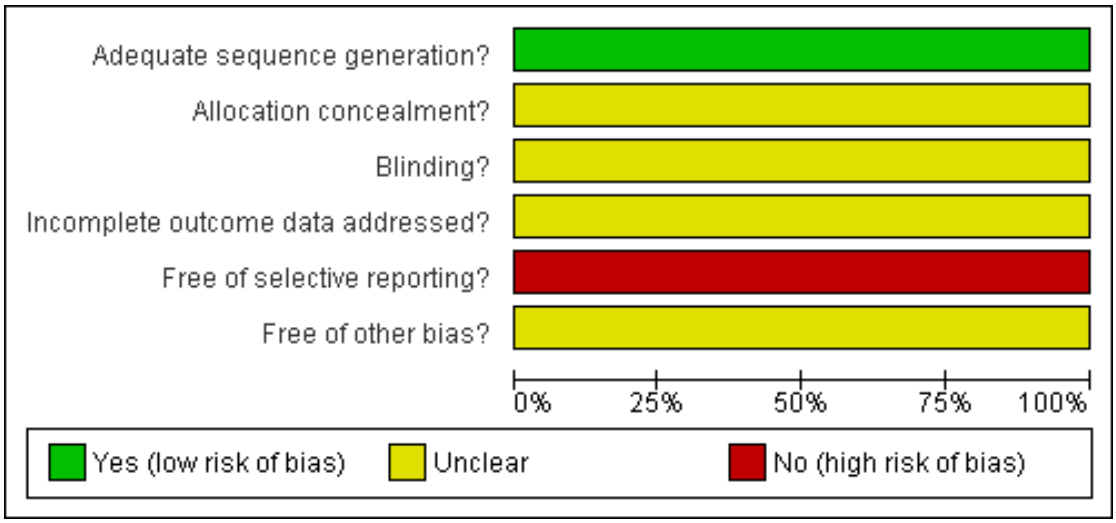
We identified one retrospective study comparing open surgical nephroureterectomy with percutaneous approach (Lee 1999). This study showed the disease-specific survival rates after open and percutaneous approaches for grade 2 disease were 53.8 and 53.3 months, respectively (P > 0.05), and concluded that the percutaneous approach should be an option in patients with solitary kidneys, patients at risk of chronic renal failure, and healthy individuals with normal contra lateral kidneys who are willing to abide by a strict and lengthy follow-up protocol.

Three studies (Dragicevic 2009; Giannarini 2007; Lucas 2009) compared nephron sparing surgery and radical nephroureterectomy ('Table 4').

Risk of bias in included studies

The only randomised controlled trial included in this review used stratified permuted randomisation technique with ratio of 1:1 for treatment allocation. For risk of bias, see 'Figure 1'.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

There was no allocation concealment in the single study included in this review. Consequently there was a high risk of reporting bias.

Blinding

No blinding of treatment allocation, intervention or outcome assessment was evident in the included trial.

Incomplete outcome data

Despite high stage and high grade tumours in ONU group, the LNU group has worse 5 year cancer specific survival rates and 5 year metastasis free survival rates (although not statistically significant). This hasn't been explained. The study does not give the absolute figures for bladder tumour free rates for the two groups.

Selective reporting

The study addressed relevant immediate and oncological outcomes.

Other potential sources of bias

The median follow up of this study was 41 months. Longer follow up will be required to establish true oncological outcomes.

Effects of interventions

See: **Summary of findings for the main comparison** Surgical mamgement for upper tract transitional cell carcinoma: Summary of findings

This review identified one RCT comparing peri-operative and oncological outcomes between laparoscopic and open nephroureterectomy (Simone 2009). This trial was a single institutional study with all procedures (both open and laparoscopic approaches) undertaken by one experienced surgeon. Forty patients with non-metastatic upper tract transitional cell carcinoma were recruited for both approaches. Peri-operative outcomes were compared using Student's t-test and oncological outcomes were compared using the log-rank test. Further analysis was performed after stratification by grade and stage. This trial showed that the laparoscopic approach had better statistically significant results for blood loss (104 mL versus 430 mL, P < 0.001) and mean time to discharge (2.30 days versus 3.65 days, p<0.001) when compared to the open approach. At a median follow up of 44 months, the overall 5 year cancer-specific survival (89.9% versus 79.8%) and 5 year metastasis-free survival rates (77.4% versus 72.5%) for the open approach were better than the laparoscopic approach, respectively, although not statistically significant.The bladder tumour free rates for the two groups were similar. However, on further stratification by stage and grade, the oncological outcomes for organ-confined disease (Stage < T3) were comparable for the two groups.

DISCUSSION

Our search strategy included a comprehensive search of electronic databases, meticulous handsearching of relevant journal articles and abstracts and personal communication with experts in uro-oncology. Therefore, it is highly unlikely that important studies have been missed.

Our study found just one randomised control trial comparing laparoscopic nephroureterectomy with open nephroureterectomy (Simone 2009).This trial showed that the laparoscopic approach had better perioperative outcomes when compared with the open approach. There was statistically significant more blood loss (104 mL versus 430 mL; P < 0.001) and longer time to discharge (2.30 days versus 3.65 days) for open surgery compared to laparoscopic approach, respectively. The oncological outcomes (bladder tumour-free survival, metastases-free survival, cancer-specific survival) at a median follow-up of 44 months, in pathologically confirmed organ-confined disease were comparable for the two groups.

We identified a number of observational studies comparing different surgical approaches to the management of TCC. However, we would strongly recommend caution in interpreting these results, given the various methodological problems with the retrospective study design, particularly the small sample sizes and their associated lack of power.

This systematic review has highlighted the paucity of good quality RCTs for surgical management of upper tact transitional cell carcinoma. This is disappointing given that several surgical procedures (in particular minimally invasive procedures) have been introduced over the past two decades in clinical practice with reported patient-based outcomes. Observational data and one small randomised trial, despite the small sample sizes, indicate that that laparoscopic approach has better early surgical outcomes, and comparable oncological outcomes in the management of upper tract TCC (Bariol 2004; Capitanio 2009; Chung 2007; Chung 2008; Gill 2000; Goel 2002; Greco 2009; Hattori 2006; Hsueh 2004; Hsueh 2007; Kawauchi 2003; Landman 2002; Li 2001; Manabe 2007; Matsui 2002; Muller 2007; Okeke 2002; Ogegawa 2006; Raman 2006; Rassweiler 2004; Stifelman 2001;Simone 2009 Taweemonkongsap 2008).

There are several documented problems in conducting a well designed randomised controlled trial for comparing surgical interventions. With the introduction of laparoscopic approach to the surgical excision of upper tract TCC with various reported advantages, at least in the in the case series and non-randomised liter-

ature, patients preference becomes the main issue. This is a potential reason for failure to recruit enough numbers to answer the research question.The operator's choices or biases towards a particular procedure, which is dependent on the operator's skill and education, are the other impeding factors. Furthermore, blinding of outcome assessors to the surgical procedures, especially if they are compared, remains a subject of methodological discussion in the surgery.

Summary of main results

In patients with localised disease, the laparoscopic approach is associated with significantly less blood loss and hospital stay which translates into better recovery from the procedure. Short term follow-up data reports no significant differences in the oncological outcomes between laparoscopic and open approach. Clinically effectiveness of laparoscopic approach in patients with locally advanced disease (T3 and suspected nodal involvement) remains to be proven.

Overall completeness and applicability of evidence

In view of the poor quality of evidence, mainly from retrospective or non-controlled studies with poor design, applicability of results to the real clinical practice are difficult to justify. The technology in the laparoscopic approach has disseminated faster than than the evidence in the surgical practice and it is unlikely that results will change the current practice.

Quality of the evidence

The overall quality of available evidence identified by this review remains poor making it difficult to make a particular recommendation for change in surgical practice of upper tract TCC.

Potential biases in the review process

The main bulk of the literature on surgical approaches in upper tract TCC comes from uncontrolled (retrospective or prospective) studies with inherent risks of selection and reporting biases.

Agreements and disagreements with other studies or reviews

A recent non-systematic review reported that the laparoscopic approach was associated with a longer operating time (277 minutes versus 200 minutes), but reduced blood loss (241 mL versus 463 mL), a reduced analgesic requirement, and a shorter hospital stay, compared to open surgery (Rassweiler 2004). From an oncological perspective, there was no statistically significant differences between the two groups for bladder recurrence (24.0% versus 24.7%), local recurrence (4.4% versus 6.3%) and distant metastasis (15.5% versus 15.2%).The 2 and 5-year survival rates for the laparoscopic and open groups were 75.2% versus 76.2%, and 81.2% versus 61%, respectively (Rassweiler 2004).
A recent multicentre retrospective study of 1249 patients with non metastatic upper tract transitional cell carcinoma compared the oncological efficacy, i.e. recurrence rate and cancer-specific mortality, between open and laparoscopic nephroureterectomy. The five-year recurrence free survival estimates were 86.8% and 76.2% for LNU and ONU, respectively. Five-year cancer-specific mortality-free survival estimates were 85.8% and 73.1% for LNU and ONU, respectively. The LNU cohort did, however, have more pathologically favourable cases. In a univariate adjusted analysis to stage and also an adjusted multivariate analysis, there was no statistical difference for recurrence and cancer specific mortality between ONU and LNU (Capitanio 2009).

AUTHORS' CONCLUSIONS

Implications for practice

Although voluminous literature exists comparing different surgical approaches for the management of upper tract TCC, the quality of the retrospective studies and the one small randomised controlled trial is poor. The conclusions of the reported literature support the early benefits (less blood loss and shorter hospital stay) of the laparoscopic approach, which is the current standard of practice in many centres around the world. This review cannot support any potential change in surgical practice of upper tract TCC due to inherent biases, poor quality of design, and reporting of the systematically reviewed studies.

Implications for research

The review has the following implications for research.

1. Future multicentre randomised controlled trials are required to assess the benefits and harms of one surgical approach over another in the management of upper tract TCC.

2. A consensus is needed for outcomes reporting, standardisation of surgical technique, and introduction of newer procedures for a disease such as upper tract TCC, where multiple approaches have been shown to be feasible and effective.

3. Qualitative research in assessing the attitudes of patients and physicians towards changes in surgical practice.

4. Need for randomised controlled trials in surgical treatment.

5. Research in surgical skills education and its influence on the outcomes of procedures.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Simone 2009

Methods	RCT
Participants	80 patients with upper tract TCC were randomised to laparoscopic or open surgical approach (1:1 ratio allocation)
Interventions	Laparoscopic (transperitoneal) approach (n = 40) Open (two incision) approach (n = 40) All surgical procedures were performed by a single surgeon
Outcomes	Operative time, blood loss, hospital stay, cancer-specific survival, bladder tumour-free survival and metastases free survival
Notes	Exclusion criteria included previous history of urothelial cancer, presence of nodal involvement, distant metastasis and coexistent bladder tumour at diagnosis

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	This review used stratified permuted randomisation technique with ratio of 1:1 for treatment allocation. The power calculation was based on the primary outcome (mean time to hospital discharge)
Allocation concealment?	Unclear	There was no allocation concealment in the single study included in this review. Consequently there was a high risk of reporting bias
Blinding? All outcomes	Unclear	No blinding of treatment allocation, intervention or outcome assessment was evident in the included trial
Incomplete outcome data addressed? All outcomes	Unclear	Despite high stage and high grade tumours in ONU group, the LNU group has worse 5 year cancer specific survival rates and 5 year metastasis free survival rates (although not statistically significant). This hasn't been explained. The study does not give the absolute figures for bladder tumour free rates for the two groups
Free of selective reporting?	No	The study address relevant immediate and oncological outcomes
Free of other bias?	Unclear	The median follow up in this study is 41 months. Longer follow up will be required to establish true oncological outcomes

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bariol 2004	No random allocation to treatment (non-randomised trial)
Capitanio 2009	No random allocation to treatment (non-randomised trial)
Chung 2007	No random allocation to treatment (non-randomised trial)
Chung 2008	No random allocation to treatment (non-randomised trial)
David 2002	No random allocation to treatment (non-randomised trial)
Dragicevic 2009	No random allocation to treatment (non-randomised trial)
Giannarini 2007	No random allocation to treatment (non-randomised trial)
Gill 2000	No random allocation to treatment (non-randomised trial)
Goel 2002	No random allocation to treatment (non-randomised trial)
Greco 2009	No random allocation to treatment (non-randomised trial)
Hattori 2006	No random allocation to treatment (non-randomised trial)
Hsueh 2004	No random allocation to treatment (non-randomised trial)
Hsueh 2007	No random allocation to treatment (non-randomised trial)
Kawauchi 2003	No random allocation to treatment (non-randomised trial)
Ko 2007	No random allocation to treatment (non-randomised trial)
Landman 2002	No random allocation to treatment (non-randomised trial)
Lee 1999	No random allocation to treatment (non-randomised trial)
Li 2001	No random allocation to treatment (non-randomised trial)
Lucas 2009	No random allocation to treatment (non-randomised trial)
Manabe 2007	No random allocation to treatment (non-randomised trial)
Matin 2005	No random allocation to treatment (non-randomised trial)
Matsui 2002	No random allocation to treatment (non-randomised trial)
Muller 2007	No random allocation to treatment (non-randomised trial)

(*Continued*)

Murphy 2002	No random allocation to treatment (non-randomised trial)
Ogegawa 2006	No random allocation to treatment (non-randomised trial)
Okeke 2002	No random allocation to treatment (non-randomised trial)
Raman 2006	No random allocation to treatment (non-randomised trial)
Rassweiler 2004	No random allocation to treatment (non-randomised trial)
Romero 2007	No random allocation to treatment (non-randomised trial)
Salvador-Bayarri 2002	No random allocation to treatment (non-randomised trial)
Stifelman 2001	No random allocation to treatment (non-randomised trial)
Taweemonkongsap 2008	No random allocation to treatment (non-randomised trial)
Walton 2009	No random allocation to treatment (non-randomised trial)

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Summary of search findings

Database	Coverage	Search date July 2008	First update December 2009	Second update July 2010	Total no. refs
MEDLINE	1950 -> present	207	19	9	235
Premedline	22.07.08	0	0	0	0
Embase	1980 ->present	157	22	9	188
Cochrane Library	No restrictions	184	5	4	193
Web of Science®	1900 -> present	411	100	33	544
AMED	1985 -> present	0	0	0	0
Cinahl	1981->present	54	24	11	89
BNI	1985 ->present	0	0	0	0
LILACS	1982-> present	2	0	0	2
Biomed Central	1997->present	35	0	3	38
BIOSIS	1926 to present	279	33	7	319
SCOPUS	1981->present	478	78	25	581
ASCO abstracts	1981 to present	6	0	1	7
Total no. refs		1813	281	102	2178
After de-duplication		1179	242	84	1505

Table 2. Table 1. Retrospecitive non-randomised studies comparing the pre-stated objectives for open and laparoscopic resection.

Study	Surgical comparisons
Bariol 2004	Laparoscopic nephroureterectomy versus open nephroureterectomy
Capitanio 2009	Laparoscopic nephroureterectomy versus open nephroureterectomy
Chung 2007	Hand Assisted Laparoscopic nephroureterectomy versus open nephroureterectomy
Chung 2008	Hand Assisted Laparoscopic nephroureterectomy versus hand-assisted retroperitoneoscopic nephroureterectomy
Dragicevic 2009	Open conservative surgery versus radical nephroureterectomy
Gill 2000	Laparoscopic nephroureterectomy versus open nephroureterectomy
Goel 2002	Laparoscopic nephroureterectomy versus open nephroureterectomy
Greco 2009	Laparoscopic nephroureterectomy versus open nephroureterectomy
Hattori 2006	Combined (LNU + Open bladder cuff excision) versus pure LNU (LNU + endoscopic bladder cuff excision) versus open nephroureterectomy
Hsueh 2004	Hand-assisted Retroperitoneoscopic Laparoscopic nephroureterectomy versus open nephroureterectomy
Hsueh 2007	Hand-assisted Laparoscopic nephroureterectomy versus open nephroureterectomy
Kawauchi 2003	Hand Assisted retroperitoneoscopic nephroureterectomy versus open nephroureterectomy
Landmann 2002	Hand-assisted laparoscopic nephroureterectomy versus standard Laparoscopic nephroureterectomy
Li 2001	Hand assisted laparoscopic nephroureterectomy versus open nephroureterectomy
Lucas 2008	Nephron sparing surgery versus nephroureterectomy
Manabe 2007	Laparoscopic nephroureterectomy versus open nephroureterectomy
Matsui 2002	Retroperitoneoscopic nephroureterectomy versus open nephroureterectomy
Muller 2007	Laparoscopic nephroureterectomy versus open nephroureterectomy
Okegawa 2006	Retroperitoneoscopic nephroureterectomy versus open nephroureterectomy
Okeke 2002	Hand assisted laparoscopic nephroureterectomy versus open nephroureterectomy
Raman 2006	Hand assisted laparoscopic nephroureterectomy versus open nephroureterectomy

Table 2. Table 1. Retrospecitive non-randomised studies comparing the pre-stated objectives for open and laparoscopic resection. (*Continued*)

Rassweiler 2004	Laparoscopic nephroureterectomy versus open nephroureterectomy
Stifelman 2001	Hand Assisted Laparoscopic nephroureterectomy versus open nephroureterectomy
Taweemonkongsap 2008	Retroperitoneoscopic nephroureterectomy versus open nephroureterectomy
Romero 2007	Extravesical laparoscopic control of the bladder cuff versus extravesical open control of the bladder cuff
Ko 2007	Open excision of a bladder cuff versus transurethral incision of the ureteral orifice (TUIUO)
Salvador-Bayarri 2002	Open excision of a bladder cuff versus endoscopic resection of ureter
Matin 2005	Extravesical laparoscopic control of the bladder cuff versus cystoscopic secured detachment and ligation method
Lee 1999	Open nephroureterectomy versus percutaneous approach
Giannarini 2007	Nephron sparing surgery versus nephroureterectomy
Walton 2009	Endoscopic ureteral detachment versus open Bladder cuff excision

Table 3. Studies comparing the various techniques of en-bloc excision of the lower ureter during nephroureterectomy procedure.

Study	Objectives	Prinicpal findings
Romero 2007	Extravesical laparoscopic control of the bladder cuff versus Extravesical open control of the bladder cuff	· The laparoscopic group was associated with an increase in the overall rate of recurrence and a shorter recurrence-free survival (not statistically significant) · Rates of local and bladder recurrence and distant metastases were similar
Ko 2007	Open excision of a bladder cuff versus Transurethral incision of the ureteral orifice (TUIUO)	· The bladder recurrence rates were similar in the OC group (22.2%; 6/27) and the TUIUO group (26.3%; 5/19) · There were no pelvic recurrences in either group
Salvador-Bayarri 2002	Open excision of a bladder cuff versus Endoscopic resection of ureter	· Bladder tumour recurrence 39% versus 34.5% · No statistical significance
Matin 2005	Extravesical laparoscopic control of the bladder cuff versus Cystoscopic secured detachment and ligation method	· Bladder tumour recurrence 41.7% versus 13.9% (not statistically significant) · Retroperitoneal Metastasis 8.3% versus 5.6% (not statistically significant)

Table 3. Studies comparing the various techniques of en-bloc excision of the lower ureter during nephroureterectomy procedure. (*Continued*)

		· Distant Metastasis 25% versus 8.3% (not statistically significant)
Walton 2009	Endoscopic ureteral detachment versus Open Bladder cuff excision	· Bladder tumour recurrence 54.4 % versus 47.9% (not statistically significant) · Recurrence free survival and disease specific survival similar for both groups

Table 4. Studies comparing outcomes of nephron sparing surgery and radical nephroureterectomy

Study	Objectives	Findings
Giannarini 2007	Distal ureter resection with bladder cuff excision and ureter re-implantation versus radical nephroureterectomy with bladder cuff excision	• Cancer specific survival at 5 and 10 years was not statistically significantly different (log-rank test, P = 0.896) • Overall survival at 5 and 10 years was not statistically significantly different (log-rank test, P = 0.693)
Dragicevic 2009	Open conservative surgery versus Radical nephroureterectomy	• 5 year survival rates 59% versus 55% • 5 year survival rates for imperative and elective indications 41% versus 75% • Radical nephroureterectomy had statistically significant poor outcomes for the disease on univariate analysis (HR = 2.2, 95% CI 1.1 to 4.6, P = 0.030)
Lucas 2008	Nephron sparing surgery versus nephroureterectomy	Low grade disease • ·5-year Overall survival 75.4% versus 66.4% P = 0.281 • ·5-year Disease Specific survival 86.2% versus 87.4% P = 0.909 High grade disease • ·5-year overall survival 45% versus 71.5% P = 0.077 • ·5-year disease-specific survival 68.6% versus 75% P = 0.528

APPENDICES

Appendix 1. Search stategies

Search strategies TCC

MEDLINE (OVID)

1. exp Carcinoma, Transitional Cell/
2. exp Ureteral Neoplasms/
3. ((upper tract or renal pelv$ or ureter$ or calice$) adj3 (urothelial or tcc or transitional or carcinoma$ or tumo?r$ or cancer$ or neoplas$)).tw.
4. or/1-3
5. exp Surgery/
6. exp nephrectomy/
7. exp partial nephrectomy/
8. nephroureterectom$.tw.
9. ((ureteral or percutaneous or surgical or ureteroscopic or endoscopic) adj3 (resection or management or fulguration)).tw.
10. (ONU or LNU).tw.
11. ((radical or open or laparoscop$) adj3 (surg$ or nephro$ or nephrec)).tw.
12. partial nephrectomy.tw.
13. exp Electrocoagulation/
14. exp Laser Therapy/
15. re-anastomosis.tw.
16. electrocaut$.tw.
17. ((segmental or bladder cuff) adj2 resection).mp.
18. or/5-17
19. 4 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. or/20-27
29. humans.sh.
30. 28 and 29
31. 19 and 30

Embase (OVID)

1. Transitional Cell Carcinoma/
2. exp Ureter Tumor/
3. ((upper tract or renal pelv$ or ureter$ or calice$) adj3 (urothelial or tcc or transitional or carcinoma$ or tumo?r$ or cancer$ or neoplas$)).tw.
4. or/1-3
5. exp SURGERY/
6. exp nephrectomy/
7. exp partial nephrectomy/
8. nephroureterectom$.tw.
9. ((ureteral or percutaneous or surgical or ureteroscopic or endoscopic) adj3 (resection or management or fulguration)).tw.

10. (ONU or LNU).tw.
11. ((radical or open or laparoscop$) adj3 (surg$ or nephro$ or nephrec)).tw.
12. partial nephrectomy.tw.
13. exp ELECTROCOAGULATION/
14. exp Low Level Laser Therapy/
15. exp Cauterization/
16. (re-anastomosis or electrocaut$).tw.
17. ((segmental or bladder cuff) adj2 resection).tw.
18. or/5-17
19. 4 and 18
20. Crossover Procedure/
21. double-blind procedure/
22. randomized controlled trial/
23. single-blind procedure/
24. (random$ or factorial$ or crossover$ or cross over$ or placebo$ or assign$ or allocat$ or volunteer$).mp.
25. ((doubl$ or singl$) adj blind$).mp.
26. or/20-25
27. 19 and 26

Cochrane Library (Wiley)

1. MeSH descriptor Carcinoma, Transitional Cell explode all trees
2. MeSH descriptor Ureteral Neoplasms explode all trees
3. (upper tract or renal pelv* or ureter* or calice*):kw,ti,ab NEAR/3 (urothelial or tcc or transitional or carcinoma* or tumor* or tumour* or cancer* or neoplasm*):kw,ti,ab
4. (#1 OR #2 OR #3)
5. MeSH descriptor Surgical Procedures, Operative explode all trees
6. MeSH descriptor Nephrectomy explode all trees
7. (nephrouereterectom* or nephrectom*):kw,ti,ab
8. (ureteral or percutaneous or surgical or ureteroscopic or endoscopic):kw,ti,ab NEAR/3 (resection or management or fulguration):kw,ti,ab
9. (ONU or LNU):kw,ti,ab
10. (radical or open or laparoscop*):kw,ti,ab NEAR/3 (surg* or nephro* or nephrec*):kw,ti,ab
11. MeSH descriptor Electrocoagulation explode all trees
12. MeSH descriptor Laser Therapy explode all trees
13. re-anastomosis:kw,ti,ab OR electrocaut*:kw,ti,ab
14. (segmental or bladder cuff):kw,ti,ab NEAR/2 (resection):kw,ti,ab
15. (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)

Web of Science

1. TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)
2. TS=(transitional cell carcinoma)
3. TS=(upper tract urothelial or renal pelvis or ureter or ureteral) SAME TS=(cancer* or carcinoma* or tumor* or tumour* or neoplas*)
4. #3 OR #2
5. TS=(surgery)
6. TS=(nephroureterectomy or resection or fulguration or electro* or laser)
7. #6 OR #5
8. #7 AND #4 AND #1

CINAHL (Ebsco)

1. (MH "Bladder Neoplasms")
2. bladder* N3 cancer*
3. bladder* N3 neoplasm*
4. ureter* N3 neoplasm*
5. ureter* N3 cancer*
6. (transitional cell) or tcc
7. S1 or S2 or S3 or S4 or S5 or S6
8. (MH "Surgery, Operative+")
9. (MH "Nephrectomy")
10. nephroureterectom* or nephrectom*
11. partial or radical or open or laparoscop*
12. resect* or fulgarat*
13. S8 or S9 or S10 or S11 or S12
14. S7 and S13
15. ((MH "Random Assignment") or (MH "Random Sample+") or (MH "Crossover Design") or (MH "Clinical Trials+") or (MH "Comparative Studies") or (MH "Control (Research)+") or (MH "Control Group") or (MH "Factorial Design") or (MH "Quasi-Experimental Studies+") or (MH "Placebos") or (MH "Meta Analysis") or (MH "Sample Size") or (MH "Research, Nursing") or (MH "Research Question") or (MH "Research Methodology+") or (MH "Evaluation Research+") or (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") or (MH "Nursing Practice, Research-Based") or (MH "Solomon Four-Group Design") or (MH "One-Shot Case Study") or (MH "Pretest-Posttest Design+") or (MH "Static Group Comparison") or (MH "Study Design") or (MH "Clinical Research+")) or (clinical nursing research or random* or cross?over or placebo* or control* or factorial or sham* or meta?analy* or systematic review* or blind* or mask* or trial*)
16. S14 and S15

British Nursing Index (OVID)

1. exp cancer/
2. exp "Urinary System and Disorders"/
3. ((bladder$ or upper tract or renal pelv$ or ureter$ or calice$) adj3 (urothelial or tcc or transitional or carcinoma$ or tumo?r$ or cancer$ or neoplas$)).tw.
4. 1 and 2
5. 3 or 4
6. exp surgery : operative/
7. (nephroureterectom$ or nephrectom$).tw.
8. ((ureteral or percutaneous or surgical or ureteroscopic or endoscopic) adj3 (resection or management or fulguration)).tw.
9. ((partial or radical or open or laparoscop$) adj3 (surg$ or nephro$ or nephrec)).tw.
10. 6 or 7 or 8 or 9
11. 5 and 10
12. Randomized controlled trial$.mp.
13. (clinic$ adj trial$1).tw.
14. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
15. (allocated adj2 random).tw.
16. placebo$.mp.
17. 12 or 13 or 14 or 15 or 16
18. 11 and 17

LILACS

(Transitional or Transicionales or Transição or tcc) and (surgery or surgical or cirurg$ or cirugi$ or quirúrg$ or nephrectom$ or nefrectom$) and (Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Ab random$ OR Ab aleator$ OR Ab placebo$ OR Mh Clinical Trials as Topic OR Ti trial)

Biomed Central

((random* OR trial* OR blind* OR placebo*)[tw]) AND ("transitional cell carcinoma"[TW] AND (surgery OR nephrectomy OR nephroureterectomy)[TW])

BIOSIS

1. TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)
2. TS=(transitional cell carcinoma)
3. TS=(upper tract urothelial or renal pelvis or ureter or ureteral) SAME TS=(cancer* or carcinoma* or tumor* or tumour* or neoplas*)
4. #2 or #3
5. TS=(surgery)
6. TS=(nephroureterectomy or resection or fulguration or electro* or laser)
7. #5 or #6
8. #1 and #4 and #7

Scopus

(TITLE-ABS-KEY("transitional cell carcinoma"))
OR (TITLE-ABS-KEY(urothelial OR tcc OR transitional) AND (carcinoma* OR tumo*r OR cancer* OR neoplas*))
AND (TITLE-ABS-KEY(surg* OR nephrectomy OR nephroureterectomy))
AND (TITLE-ABS-KEY(random* OR trial* OR blind* OR placebo*))

AMED (OVID)

1. exp Bladder neoplasms/
2. ((bladder$ or upper tract or renal pelv$ or ureter$ or calice$) adj3 (urothelial or tcc or transitional or carcinoma$ or tumo?r$ or cancer$ or neoplas$)).tw.
3. 1 or 2
4. exp Surgery/
5. (nephroureterectom$ or nephrectom$).tw.
6. ((ureteral or percutaneous or surgical or ureteroscopic or endoscopic) adj3 (resection or management or fulguration)).tw.
7. ((partial or radical or open or laparoscop$) adj3 (surg$ or nephro$ or nephrec)).tw.
8. 4 or 5 or 6 or 7
9. 3 and 8
10. exp Randomized controlled trials/
11. (clinic$ adj trial$1).tw.
12. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.
13. (allocated adj2 random).tw.
14. placebo$.mp.
15. 10 or 11 or 12 or 13 or 14
16. 9 and 15

WHAT'S NEW

Last assessed as up-to-date: 5 September 2010.

Date	Event	Description
8 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 4, 2011

Date	Event	Description
21 February 2008	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Ghulam Nabi (GN) and Mike Shelley (MS) were responsible for the concept of this review. Bernadette Coles developed, ran and updated the search strategies. Study identification, data extraction, data analysis, manuscript preparation were performed by Bhavan Rai (BR) and Ismail El-Mokadem (IE). Chandra S Biyani (CSB); Mike Shelley (MS) and Ghulam Nabi (GN) critically reviewed the contents of this review. All authors approved the final version of the study.

DECLARATIONS OF INTEREST

The authors declare no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Velindre NHS Trust, Cardiff, UK.

External sources

- Cancer Research Wales, UK.

Funded library facilities

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol, the methods for performing a meta-analysis were described. Since no meta-analysis was possible with the available data, the respective sections have been deleted.

INDEX TERMS

Medical Subject Headings (MeSH)

Carcinoma, Transitional Cell [*surgery]; Kidney Neoplasms [*surgery]; Laparoscopy [*methods]; Nephrectomy [*methods]; Randomized Controlled Trials as Topic; Ureter [surgery]; Ureteral Neoplasms [*surgery]

MeSH check words

Adult; Humans