Original Article

Clinical Outcomes of Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma in a Specialized Cancer Hospital of a Developing Country

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(When this study was conducted, all the listed authors were working in Shaukat Khanum Cancer Hospital, Lahore and participated in study. However, after that they are promoted and current affiliation are as mentioned above)

Abstract

Background: Radical nephroureterectomy (RNU) remains the standard of care for managing upper tract urothelial carcinoma (UTUC). Various techniques and approaches for RNU have been practiced, yielding variable outcomes. In this study, we describe our technique of a combined endoscopic and open single-incision radical nephroureterectomy with bladder cuff.

Objective: To determine outcomes of open radical nephroureterectomy (RNU) using the 'pluck' technique, in patients with localized upper tract urothelial carcinoma (UTUC).

Methods: After approval from the institutional review board, the data of all upper tract urothelial carcinoma patients operated from January 2012 to June 2022 at Shaukat Khanum Memorial Cancer Hospital and Lahore General Hospital, Lahore was reviewed retrospectively. Studied variables were; Demographic characteristics, medical comorbidities, presenting concerns, and preoperative and postoperative tumour characteristics. Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 25.0

Results: Out of the 31 included patients, the renal pelvic tumours were the commonest, noted in 18 (58.1%), and commonest stage being T2, present in 13 (41.9%) patients. During median follow up of 48 months (range, 3 to 132), 10 patients developed disease recurrence and 6 patients died during the median time of 39 months (range, 3 to 64). Estimated mean recurrence-free and overall survival was 82.10 ± 10.01 months and 114.40 ± 11.30 months, respectively. No major peri-operative complications were recorded. Five-year disease-free survival and overall survival was calculated to be 72% and 70%, respectively.

Conclusion: Open Radical nephroureterectomy using the pluck technique is a safe and effective surgical option in treating patients presenting with localized upper urinary tract urothelial carcinoma.

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Introduction

The urinary tract is lined by transitional epithelium, starting from the calyceal system of one kidney, all the way through the ureter, bladder and urethra to

the contralateral ureter and kidney.[1] Thus, the lining of the urinary tract can be considered as one single unit and urothelial cancer affecting one site poses a risk to any other region, to varying degrees, by the process of field cancerization. Upper tract urothelial carcinoma (UTUC) is a rare disease entity, diagnosed in 0-3.5% patients presenting with haematuria.[2] It comprises 5-10% of all urothelial carcinoma with an estimated annual incidence in Western countries of around 2 cases per 100,000 inhabitants.[3] This cancer has doubled the propensity to involve the Pyelocaliceal system as compared to the ureters. In 17% of cases, a synchronous bladder cancer is present.[4] Metachronous tumour in the bladder occurs in 22-47% of UTUC patients.[5] On the other hand, in 2-6% cases, the contralateral upper tract cancer occurs in patients with a previous history of UTUC. Although less common, generally, UTUC is found to be more aggressive, as compared to its bladder counterpart as 60% of the former are invasive as compared to 15-25% of the later at the time of diagnosis, and 7% have metastasized.[6] This leads to the concept that the urothelium lining the renal pelvis and ureter, although a single continuous unit, is basically different both phenotypically and genotypically from that lining the bladder and these differences are present even at the embryonal and molecular level.[7]

The standard surgical treatment of the UTUC is radical nephroureterctomy (RNU), which encompasses enblock extirpation of the kidney and ureter, along with resection of a cuff of the bladder wall all around the ureteric opening.[8] With the current trend of nephron preservation, while still achieving adequate tumour control, as observed in the form of partial nephrectomy for renal tumour, various alternative surgical, endoscopic and percutaneous treatment options have been advocated by different authors for UTUC as well, with variable results.[9,10] However, RNU remains the standard of care, unless kidney preservation is necessary because of a single renal unit or compromised renal function. There are different techniques of dismembering the ureter from the bladder. The choice remains controversial as various techniques have been advocated by different authors.[11,12,13] In this study, we present the experience in terms of survival outcomes of patients undergoing RNU at our institution.

Methods

We retrieved the medical records of all patients undergoing treatment for upper tract urothelial cancer from the hospital information system. All patients with ages of 18 years or more, undergoing RNU using the pluck technique, since January 2012 through June 2022 were included in the study. Patients with a history of muscle invasive bladder cancer or another primary cancer were excluded from the study.

In our centre, we performed a pluck technique in dealing with the distal ureter. After the transurethral incision of the ureteric orifice, with an adequate margin of the surrounding bladder wall and exposure of the perivesical fats, the bladder was placed on free drainage using 18fr catheter. Open nephrectomy was completed using subcostal transperitoneal approach with early ligation of ureter to avoid spillage of tumor cell during nephrectomy. The ureter is dissected down, initially under vision and then blindly using the index finger sliding along its side up to its attachment with the peri vesical tissues. Since the ureter is already dissected free, it is conveniently plucked and retrieved. Complete excision of the ureter is ensured by inspecting the resected free end of the ureter

We have presented the demographic characteristics, medical comorbidities, presenting concerns, and preoperative and postoperative tumour characteristics. Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY). Continuous variables were stated as mean ± standard deviation, and categorical variables were computed as frequencies and percentages. The Kaplan-Meier method was used to estimate survival. Approval for the study was obtained from the Institutional Review Board before commencing data collection.

Results

A total of 34 patients underwent RNU during the study period. Three patients were excluded based on the mentioned criteria. Seven patients (22.5 %) had a history of non-muscle invasive bladder tumour. The common tumour location was renal pelvis, noted in 18 (58.1%) of the 31 patients. The patients' details at presentation and the clinical tumour characteristics are given in Table-1.

The most common pathological tumor stage was Stage T2, present in thirteen (41.9%) patients, followed by T1 in nine (29.0%), Ta in seven (22.6%) and T3 in one (3.2%) patient. One patient had received neoadjuvant chemotherapy and the final histology revealed no residual cancer. Ureteric margins were positive in five (16.1%) and one (3.2%) patient had positive lymph nodes on histology (Table-2).

There were no high-grade complications recorded, requiring intervention and no patient suffered perioperative mortality. The median follow-up duration was 48 months (range, 3 to 132). The patients were follo-

Table 1: *Preoperative Patients and Tumor Characteristics*

Variables	Categories	Total=N*(%)
Patients Characteristics		
Age (years)	**Mean ± standard deviation**	**55.40 ± 5.08**
Sex	Male	26 (83.9%)
	Female	5 (16.1%)
Comorbidity	None	14 (45.2%)
	HTN	12 (38.7%)
	DM	5 (16.1%)
Presentation	Hematuria	27 (87.1%)
	Pain	4 (12.9%)
Tumor Characteristics		
Tumor location	Renal Pelvis TCC	18 (58.1%)
	Ureter TCC	13 (41.9%)
Hx TCC	No	24 (77.4%)
	Yes	7 (22.6%)
cT	a/1	23 (74.2%)
	2	7 (22.6%)
	3	1 (3.2%)
cN	N0	29 (93.5%)

Table 2: *Post-operative tumor characteristics*

Complaints	Categories	Total = N (%)
Pathological T-stage	T0	1 (3.2%)
	Ta	7 (22.6%)
	T1	9 (29.0%)
	T2	13 (41.9%)
	T3	1 (3.2%)
Pathological N-stage	Nx	1 (3.2%)
	N0	29 (93.5%)
	N1	1 (3.2%)
Grade	Gx	1 (3.2%)
	Low	3 (9.7%)
	Intermediate	3 (9.7%)
	High	24 (77.4%)
Margins	Negative	26 (83.9%)
	Positive	5 (16.1%)

wed in general at 6 month post-operative CT scan, followed by yearly scans, and further imaging performed as needed based on patients' presentations. They were also followed with 3 monthly cystoscopy for the first 2 years and 6 monthly thereafter. Overall, recurrence was encountered in 10 patients. Of these, one patient developed muscle invasive bladder cancer (MIBC). The median time to the appearance of metastatic recurrence was 18 months (range, 1 to 44). The patients' details recorded during follow up are summarized in Table-3.

Table 3: *Postoperative patients' characteristics*

Variables	Categories	Total=N*(%)
Recurrence	No	21 (67.7%)
	Yes	10 (32.3%)
Site of Recurrence/ Metastasis	None	21 (67.7%)
	Lung	2 (6.5%)
	Liver	1 (3.2%)
	Bone	1 (3.2%)
	Lymph Nodes	1 (3.2%)
	Multiple sites	4 (12.9%)
	MIBC	1 (3.2%)
Treatment of Recurrence	None	24 (77.4%)
	Chemotherapy	1 (3.2%)
	Radiotherapy	1 (3.2%)
	Multimodality treatment	5 (16.1%)
Present Status	Alive	24 (77.4%)
	Loss to follow up	1 (3.2%)
	Death	6 (19.4%)
Cause of Death	Tumor progression	5 (16.1%)
	Non Cancer	1 (3.2%)

A total of 6 patients died during the follow up period. Out of these patients, 5 passed away because of the disease progression while one patient due to other medical condition. The median time to death was found to be 39 months (range, 3 to 64). The mean recurrence-free survival was 82.10 ± 10.01 months while the mean overall survival was 114.40 ± 11.30 months. The projected five-year disease-free survival and overall survival was calculated to be 72% and 70%, respectively (Figure 1).

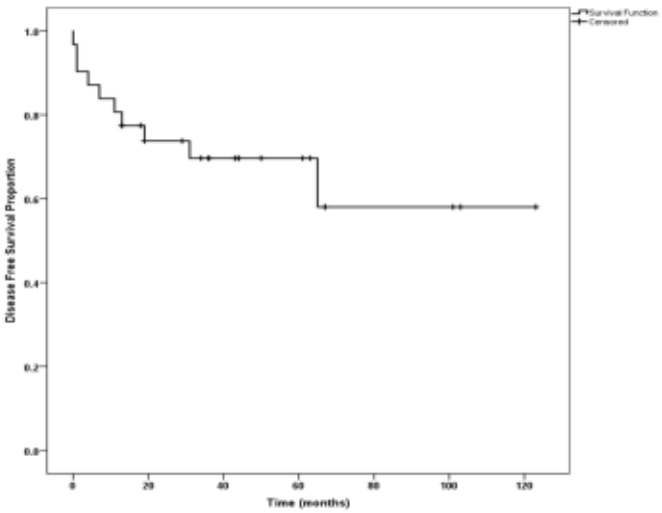

Figure 1: *Disease free survival Graph*

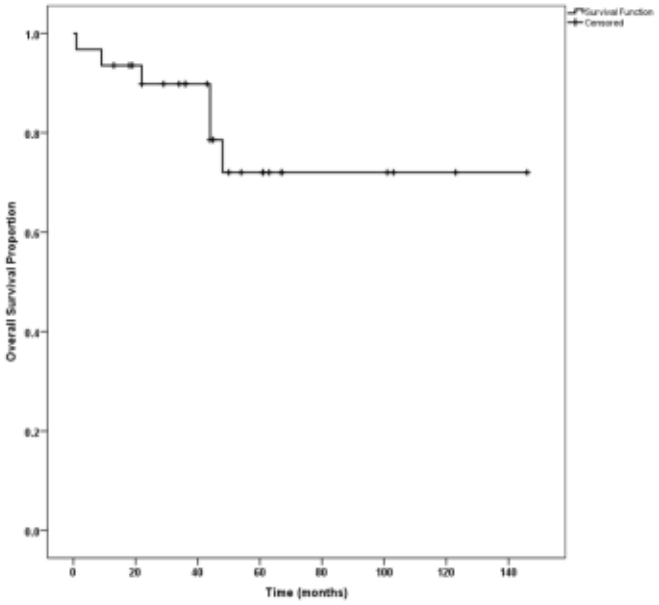

Figure 2: *Overall Survival Graph*

Discussion

UTUC is a rare disease entity and various aspects of its treatment have still not been standardized yet. These include the perioperative systemic therapy, post-operative intra-vesical mitomycin, the advantage of adjuvant chemotherapy and the technique employed in dealing with the distal ureter.[14]

Radical nephroureterectomy (RNU) with cuff of urinary bladder is gold standard in management of UTUC. RNU may be performed laparoscopically, robotic assisted laparoscopy or by conventional open surgical approach. The optimal techniques of excising the distal ureter and bladder cuff during nephroureterectomy are still evolving.[15] These include the open excision, laparoscopic stapling, lap- assisted transvesical technique, intussusception technique and pluck techniques. None of them have yet been standardized and in many instances, this method depends on the surgeon's preference or experience.

Traditionally, two separate incisions or a long midline incision from xiphisternum to pubis bone is made for open radical nephroureterectomy and excision of distal ureter with cuff of urinary bladder. This leads to more pain experienced by patient with prolonged hospital stay. We used pluck technique in dealing with the distal ureter with single subcostal incision for radical nephroureterectomy. This modification avoids a second incision, to retrieve the distal ureter, thus saving from its associated morbidity. This second incision and pelvic dissection may be difficult in obese patients and in patients with previous radiotherapy or pelvic surgery. There may be injury to the contralateral ureter more if it is not under vision. It is also much labour intensive as it may involve division of superior vesical artery and bladder mobilization

If nephrectomy is performed laparoscopically, a lower midline, Gibson or modified Pfannenstiel incision is used to deliver the whole specimen as well with open distal ureterctomy. The oncologic control of different technique has been studied by various authors. Hyunsoo Ryoo et al. in his article compared extravesical ureter ligation with transvesical resection and showed significantly higher intravesical recurrence free survival in transvesical resected group.[16] The study by Huang et al. showed increase recurrence when open bladder cuff excision was performed, but study by Toussi et al. showed no difference in oncological outcome when extravesical versus intravesical was compared.[17,18] Another technique, popularized by the Cleveland clinic, involves trans-vesical laparoscopically assisted technique for the retrieval of the distal ureter. A ureteric catheter is passed into the ureter and using laparoscopically placed two 5mm trans-vesical ports, a 5mm circumferential endoloop is tied around the end of ureter. The ureteric orifice is dissected using Collins knife up to the surrounding peri-ureteric attachments. The ureteric catheter is removed, and the loop is tied, closing the ureter. The endoloop is cut short and used as a tag for the ureteric end. Rest of the laparoscopic nephrectomy and dissection of remaining ureter is completed conventionally. Despite long learning curve, laparoscopic technique has proved to have good oncologic control in different series.[19]

The benefits of total laparoscopic nephroureterectomy with laparoscopic excision of bladder cuff are shorter operative time and shorter hospital stay. Another technique is laparoscopic stapling of the distal ureter and bladder, which is often combined with cystoscopic unroofing of the intramural ureter. Laparoscopic dissection of the distal ureter ends with the stapling of the distal ureter. The drawbacks of this procedure involve higher risk of positive margins and exposure of staples within the bladder predisposing to stone formation.[20] The intussusception technique involves antegrade passage of ureteric catheter through the ureter at the time of nephrectomy, into the bladder and tying it up with the ureteric wall. The bladder cuff is separated with the Collin knife and the ureteric catheter is pulled into the bladder, telescoping the ureter into the bladder, which is retrieved through the urethra. This technique involves the risk of exposing the ureteric mucosa to the bladder and is contraindicated in patients with tumours

involving the ureter. [21]

The theoretical drawback of our technique may be the risk of tumour cell spillage after the ureter is dissected free of the bladder attachment but clipping the ureter early during nephrectomy may reduce the spillage. Fragkoulic et al concluded in his study that endoscopic approach in management of distal ureter and ureteric orifce is non inferior to other approaches regarding oncological outcome.[22] In our series local recurrence as MIBC was seen only in a single patient, who was treated with chemoradiotherapy. Piszczek et al concluded in his meta-analysis that local recurrence and long-term survival was like those observed in laparoscopic and open methods[23]. The distant metastatic disease observed in our series is not inferior to the studies by other authors as well. In a study by Margulis, the 5-year recurrence-free and cancer-specific survival of 69% ± 1% and 73± 1% was observed. In our sturdy five year disease free survival and overall survival was 72% and 70%. Limitations of our study are small cohort of patients with retrospective data.

Conclusion

Open radical nephroureterectomy using a less morbid, single incision 'pluck' technique is safe and has reasonable survival outcomes. In settings where the laparoscopic technique is not commonly available, it can be safely offered to patients with localized upper tract urothelial carcinoma.

Ethical Approval: The Institutional Review Board, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore approved this study.

Conflict of Interest: The authors declare no conflict of interest.

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Authors' Contribution

AA: Conception & design, drafting of article, critical revisions, final approval of the version to be published

MAIK: Acquisition of data, analysis & interpretation of data, critical revision

NK: Acquisition of data, critical revision

SF: Acquisition of data, critical revision

SA: Acquisition of data, critical revision

KM: Acquisition of data, analysis & interpretation of data, critical revision

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