The impact of method of distal ureter management during radical nephroureterectomy on tumour recurrence

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Abstract

Introduction: Radical nephroureterectomy for upper tract urothelial carcinoma (UTUC) must include some form of distal ureter management to avoid high rates of tumour recurrence. It is uncertain which distal ureter management technique has the best oncologic outcomes. To determine which distal ureter management technique resulted in the lowest tumour recurrence rate, we analyzed a multi-institutional Canadian radical nephroureterectomy database.

Methods: We retrospectively analyzed patients who underwent radical nephroureterectomy with distal ureter management for UTUC between January 1990 and June 2010 at 10 Canadian tertiary hospitals. Distal ureter management approaches were divided into 3 categories: (1) extravesical tenting for ureteric excision without cystotomy (EXTRAVESICAL); (2) open cystotomy with intravesical bladder cuff excision (INTRAVESICAL); and (3) extravesical excision with endoscopic management of ureteric orifice (ENDOSCOPIC). Data available for each patient included demographic details, distal ureter management approach, pathology and operative details, as well as the presence and location of local or distant recurrence. Clinical outcomes included overall recurrence-free survival and intravesical recurrence-free survival. Survival analysis was performed with the Kaplan-Meier method. Multivariable Cox regression analysis was also performed.

Results: A total of 820 patients underwent radical nephroureterectomy with a specified distal ureter management approach at 10 Canadian academic institutions. The mean patient age was 69.6 years and the median follow-up was 24.6 months. Of the 820 patients, 406 (49.5%) underwent INTRAVESICAL, 316 (38.5%) underwent EXTRAVESICAL, and 98 (11.9%) underwent ENDOSOPIC distal ureter management. Groups differed significantly in their proportion of females, proportion of laparoscopic cases, presence of carcinoma in situ and pathological tumour stage ($p < 0.05$). Recurrence-free survival at 5 years was 46.3%, 35.6%, and 30.1% for INTRAVESICAL, EXTRAVESICAL and ENDOSCOPIC, respectively ($p < 0.05$). Multivariable Cox regression analysis confirmed that INTRAVESICAL resulted in a lower hazard of recurrence compared to EXTRAVESICAL and ENDOSCOPIC. When looking only at intravesical recurrence-free survival (iRFS), a similar trend held up with INTRAVESICAL having the highest iRFS, followed by ENDOSCOPIC and then EXTRAVESICAL management ($p < 0.05$). At last follow-up, 406 (49.5%) patients were alive and free of disease.

Conclusion: Open intravesical excision of the distal ureter (INTRAVESICAL) during radical nephroureterectomy was associated with improved overall and intravesical recurrence-free survival compared with extravesical and endoscopic approaches. These findings suggest that INTRAVESICAL should be considered the gold standard oncologic approach to distal ureter management during radical nephroureterectomy. Limitations of this study include its retrospective design, heterogeneous cohort, and limited follow-up.

Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a neoplasm arising from the urothelial cells of the renal calyces, renal pelvis, or ureter.[1] UTUC is a rare disease, with an estimated annual incidence of 1 to 2 cases per 100 000 inhabitants in Western countries.[2] It accounts for 5% to 10% of urothelial carcinomas.[3-5]

Radical nephroureterectomy with bladder cuff excision is the gold standard for the treatment of non-metastatic UTUC.[2,6] In one multi-institutional series, radical nephroureterectomy for pT1, pT2, pT3 and pT4 disease resulted in a 5-year cancer-specific survival of 91, 75, 54 and 12%, respectively.[5] The importance of appropriate distal ureter management is demonstrated in classic series where the bladder cuff and distal ureter were not removed during radical nephroureterectomy, resulting in recurrence rates of 33% to 75% in the ureteric remnant.[7-12] This likely occurs due to either antegrade seeding of the ureteric stump or panurothelial susceptibility within the entire upper urinary tract.[13] These high recurrence rates in the distal ureteric stump mirror the rates of metachronous intravesical recurrence after UTUC—presumably by similar mechanisms.[1]

The oncologic principles of distal ureter management include the excision of the entire intramural ureter and ureteric orifice with a surrounding bladder cuff.[14] This goal may be accomplished by several techniques. The intravesical technique involves a cystotomy with an intravesical excision of the ureteric orifice and intravesical ureter. This technique allows for removal of the entire distal ureter, including the ureteric orifice and surrounding bladder cuff but necessitates the morbidity of a cystotomy. The extravesical technique involves dissecting the distal ureter extravesically, tenting it away from the bladder and contralateral orifice, then excising the distal ureter and bladder cuff. The extravesical technique avoids a cystotomy, but risks an incomplete removal of the distal ureter or damage to the contralateral distal ureter. Endoscopic management of the distal ureter involves some cystoscopic confirmation that the ureteric orifice has been removed with the remainder of the ureter removed extravesically, en-bloc with the specimen. Endoscopic techniques may involve resecting the ureteric orifice down to perivesical fat or transurethrally incising around the ureteric orifice and occluding the free orifice with an Endoloop (Ethicon, Cincinnati, OH).

The most appropriate technique for distal ureter management during radical nephroureterectomy is not well-established. In efforts to expand this literature, we present an analysis of these distal ureter management techniques based on a separate multi-institutional Canadian radical nephroureterectomy collaboration.

Methods

Patients who underwent radical nephroureterectomy with distal ureter management for UTUC between January 1990 and June 2010 at 10 Canadian tertiary hospitals were retrospectively analyzed in a pooled database. Institutional review board approval for this study was obtained.

In this series, selection criteria for open or laparoscopic approach, distal ureter management method, extent of lymphadenectomy and receipt of perioperative chemotherapy were not defined a priori. Radical nephroureterectomy was performed en bloc with distal ureter management according to oncologic principles. Distal ureter management approaches were categorized as follows: (1) extravesical ureter (EXTRAVESICAL); (2) open intravesical (INTRAVESICAL); and (3) endoscopic (ENDOSCOPIC).

The EXTRAVESICAL approach involved extravesical dissection of the intramural ureter with tenting of the dissected ureter away from the bladder. The distal ureter was excised in the EXTRAVESICAL technique without opening the bladder at another location. The INTRAVESICAL method was performed after radical nephroureterectomy via a Gibson or Pfannenstiel incision and included cystotomy with intravesical excision of a bladder cuff around the intramural ureter and ureteric orifice. The bladder was then closed with absorbable sutures. The ENDOSCOPIC technique was performed prior to nephrouretectomy and consisted of endoscopic incision of a cuff of bladder surrounding the ureteric orifice using a Collings knife; a single needlescopically (5 mm) applied transvesical endoloop was used to occlude the distal ureter and prevent distal seeding. The distal ureter and bladder cuff were then removed extravesically, en bloc with the nephroureterectomy specimen.

Pathologic assessment was performed locally at each tertiary care institution and involved specialized local pathologic review for equivocal cases. Staging was performed according to the 2002 American Joint Committee on Cancer Tumor Node and Metastases staging system for UTUC.[15] Grading was performed according to the 1998 World Health Organization/International Society of Urologic Pathology consensus.[16]

Follow-up included history, physical examination, basic bloodwork, urinalysis and cytology, chest imaging, cystoscopy and computed tomography urograms. These were performed at intervals of 3 to 6 months initially and then yearly after the initial 2 to 3 years. Additional imaging was obtained when clinically indicated.

Data collected included patient age, distal ureter management approach, tumour location, laparoscopic or open approach, pT stage, grade, presence of concomitant carcinoma in situ, surgical margin status, receipt of perioperative chemotherapy, multifocality, tumour architecture, lymphovascular invasion, nodal status, and location of local or distant recurrence.

Clinical outcomes available included overall recurrence-free survival (RFS) and intravesical recurrence-free survival (iRFS). Overall recurrent disease included recurrences within the bladder, as well as contralateral recurrences, ureteric stump recurrences and distant metastatic disease arising during follow-up. Intravesical recurrences included recurrences within the bladder only.

Survival analysis was performed to determine the relationship between distal ureter management and clinical outcomes by Kaplan-Meier method and differences in survival evaluated by the log-rank test. Cox proportional regression analysis was used to determine hazard ratios with 95% confidence intervals (CI) relating distal ureter management method and RFS. Variables with a p value <0.30 on univariate analysis, defined a priori, were included in the multivariable Cox analysis. A Chi-squared test or t-test was used to evaluate differences in baseline attributes. For all statistical tests, two-tailed p values less than 0.05 were considered significant. Statistical analyses were performed using the SAS (version 9.2) statistical software package (SAS Institute Inc., Cary, NC).

Results

Between 1990 and 2010, 820 patients underwent radical nephroureterectomy with a specified distal ureter management at 10 Canadian academic institutions. The mean patient age was 69.6 years and 36.6% were female. The median follow-up was 24.6 months (Q1: 8.2 months, Q3: 56.9 months).

At last follow-up, 406 (49.5%) patients were alive and free of disease. There were 197 (24.0% of total) patients known to have died, of which 136 (16.6% of total) died from disease. A total of 284 (34.6%) patients had some form of disease recurrence during follow-up, of which 166 (20.2%) had recurrence within the bladder.

Of the total 820 patients, 406 (49.5%) patients underwent INTRAVESICAL, 316 (38.5%) underwent EXTRAVESICAL, and 98 (11.9%) underwent ENDOSOPIC management of the distal ureter during radical nephroureterectomy. We noted patient and clinicopathologic details stratified by distal ureter management technique (Table 1). Groups differed significantly in their proportion of females, proportion of laparoscopic cases, presence of carcinoma in situ and pathological tumour stage ($p < 0.05$).

The total number of recurrences in the INTRAVESICAL, ENDOSCOPIC and EXTRAVESICAL groups were 134, 38, and 112 respectively. RFS for INTRAVESICAL, ENDOSCOPIC, and EXTRAVESICAL at 2 years were 61.6%, 55.7%, and 49.6%, respectively ($p < 0.05$). At 5 years the RFS was 46.3%, 35.6%, and 30.1% for INTRAVESICAL, EXTRAVESICAL and ENDOSCOPIC, respectively ($p < 0.05$). Accordingly, INTRAVESICAL significantly improved RFS compared to EXTRAVESICAL ($p < 0.0001$) and ENDOSCOPIC ($p = 0.0006$) (Fig. 1). ENDOSCOPIC also significantly improved RFS compared to EXTRAVESICAL ($p = 0.0166$), but was inferior to INTRAVESICAL ($p = 0.0006$) (Fig. 1).

In multivariable Cox regression analysis, ENDOSCOPIC was associated with worse RFS (hazard ratio [HR] 1.488,

Table 1. Attributes of included patients stratified by distal ureter management

Attribute		Distal ureter management				p value
		EXTRAVESICAL (n=316)	INTRAVESICAL (n = 406)	ENDO (n = 98)	All (n = 820)	
Mean age (SD), years		69.9 (11.3)	69.2 (10.5)	70.0 (11.0)	69.6 (10.9)	0.96
% Female		42.1%	32.0%	38.1%	36.6%	0.02
Laparoscopic (%), n		150 (47.5%)	205 (50.5%)	83 (84.7%)	438 (53.4%)	<0.01
Perioperative chemotherapy (%), n		41 (13.0%)	43 (10.6%)	7 (7.1%)	91 (11.1%)	0.23
Tumour location (%), n	Renal pelvis	170 (53.8%)	205 (50.5%)	57 (58.2%)	432 (52.7%)	0.54
	Ureter	69 (21.8%)	107 (26.4%)	22 (22.4%)	198 (24.1%)	
	Renal pelvis and ureter	69 (21.8%)	89 (21.9%)	18 (18.4%)	176 (21.5%)	
Mixed or non-UC histology (%), n		11 (3.5%)	15 (3.7%)	6 (6.1%)	32 (3.9%)	0.47
High grade (%), n		206 (65.2%)	261 (64.3%)	58 (59.2%)	525 (64.0%)	0.64
CIS (%), n		76 (24.1%)	105 (25.9%)	12 (12.2%)	193 (23.5%)	0.02
PSM (%), n		32 (10.1%)	39 (9.6%)	10 (10.2%)	81 (9.9%)	0.95
Multifocality (%), n		82 (25.9%)	100 (24.6%)	30 (30.6%)	212 (25.9%)	0.52
Papillary architecture (%), n		254 (80.4%)	350 (86.2%)	89 (90.8%)	693 (84.5%)	0.40
LVI (%), n		212 (67.1%)	301 (74.1%)	61 (62.2%)	574 (70.0%)	0.54
pT stage	<2	127 (40.2%)	202 (49.8)	47 (50.0 %)	376 (45.9%)	0.02
	2	51 (16.1%)	57 (14.0%)	17 (17.3%)	126 (15.4%)	
	3	69 (21.8%)	89 (21.9%)	23 (23.5%)	181 (22.1%)	
	4	25 (7.9%)	11 (27.1%)	4 (4.1%)	40 (4.9%)	
Nodal metastases	Absent	59 (18.7%)	87 (21.4%)	22 (22.4%)	168 (20.5%)	0.45
	Present	25 (7.9%)	26 (6.40%)	3 (3.1%)	54 (6.6%)	
	Unknown	232 (73.4%)	293 (72.2%)	73 (74.5%)	598 (72.9%)	

Differences between groups are evaluated with the student's t-test or chi-squared test with a two-tailed p value less than 0.05 defining significance. SD: standard deviation; EXTRAVESICAL: extravesical ureter; INTRAVESICAL: open intravesical; ENDO: extravesical and endoscopic intravesical; UC: urothelial carcinoma; CIS: carcinoma in situ; PSM: positive surgical margin; LVI: lymphovascular invasion; pT: pathological tumour.

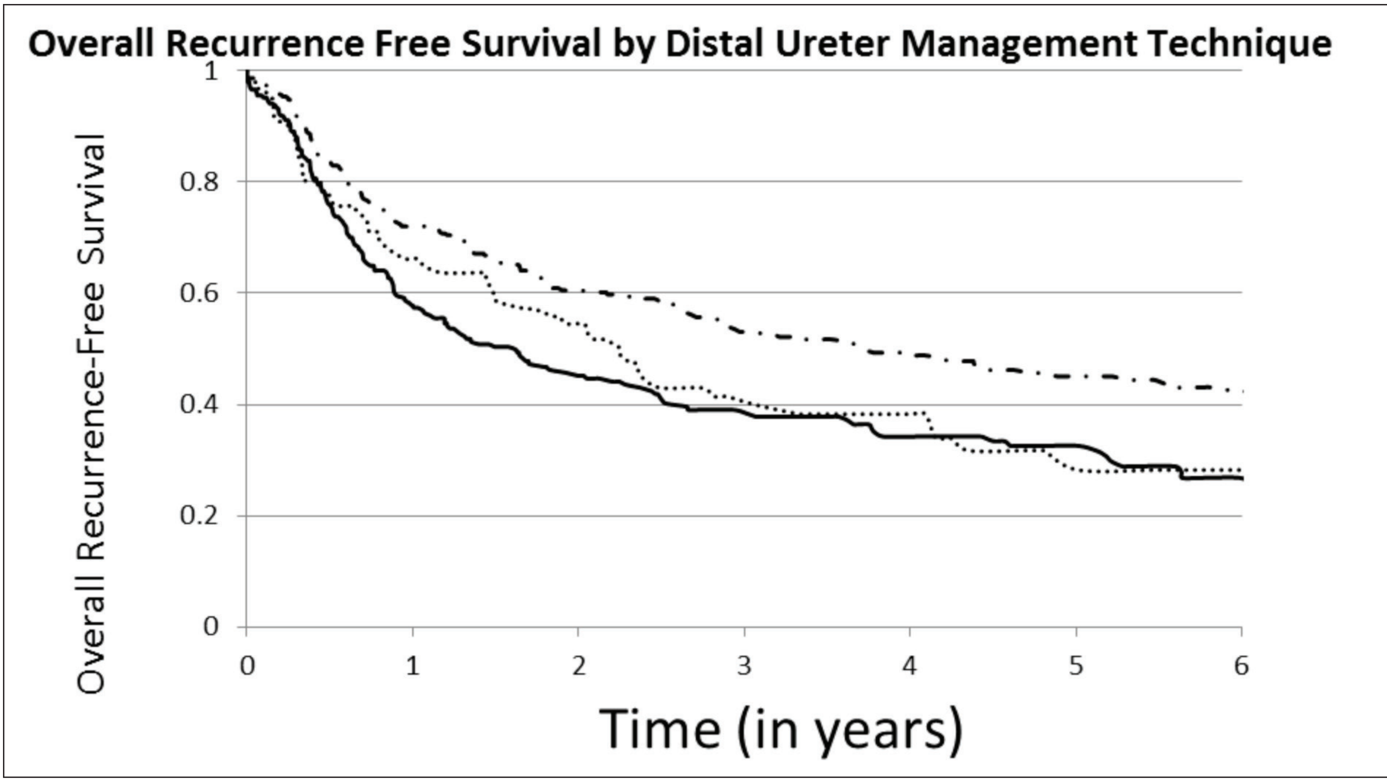

Fig. 1. Recurrence-free survival of patients undergoing radical nephroureterectomy over time, stratified by distal ureter management method. Survival analysis is performed with the Kaplan-Meier method using a log-rank test to evaluate for significant differences. P values less than 0.05 are regarded as significant. EXTRAVESICAL: extravesical excision of distal ureter; INTRAVESICAL: cystotomy with open intravesical excision of ureteric orifice and distal ureter; ENDOSCOPIC: extravesical technique with endoscopic method to ensure adequate removal of distal ureter and ureteric orifice; RFS: recurrence-free survival; SE: standard error; long dash line: INTRAVESICAL; dotted line: ENDOSCOPIC; solid line: EXTRAVESICAL.

95% CI 1.014-2.185, $p = 0.0424$) relative to INTRAVESICAL (Table 2). INTRAVESICAL was also associated with superior RFS relative to EXTRAVESICAL (HR 0.628, 95% CI 0.491-0.801, $p = 0.0002$). On multivariable analysis, RFS did not differ between EXTRAVESICAL and ENDOSCOPIC (HR 0.916 95% CI 0.633-1.327) (Table 2).

Other predictors of worsened RFS (HR >1, $p < 0.05$) on multivariable analysis included ureteric and renal tumours, positive surgical margins, receipt of perioperative chemotherapy, and nodal status (Table 2). There was a trend towards worsened RFS with lymphovascular invasion ($p = 0.0591$, HR 1.412 95% CI, 0.987-2.021) and tumour multifocality ($p = 0.0889$, HR 1.331, 95% CI 0.958-1.849).

The total number of bladder recurrences for INTRAVESICAL, ENDOSCOPIC and EXTRAVESICAL was 66, 23 and 77, respectively. When looking only at iRFS, a similar trend held up with INTRAVESICAL having the highest iRFS, followed by ENDOSCOPIC and then EXTRAVESICAL management (Fig. 2). Neither positive margin status nor the distribution of sites of recurrences differed significantly between distal ureter management groups (Table 1, Table 2).

Discussion

In this study, we have found that an open intravesical approach to distal ureter management (INTRAVESICAL) was associated with an improved RFS and iRFS compared to both extravesical (EXTRAVESICAL) and endoscopic (ENDOSCOPIC) approaches. We postulate that incomplete distal ureteric resections within the EXTRAVESICAL group account for our finding of poorer RFS compared to INTRAVESICAL. It is easy to misperceive the end of the distal ureter and perform an oncologically suboptimal bladder cuff excision, particularly in patients where exposure is difficult (e.g., an obese patient) and the excision is limited due to concerns about excising the contralateral ureteric orifice. Postoperative surveillance guidelines[17] recommend a surveillance cystoscopy at 3 months after radical nephroureterectomy, and an incomplete distal ureteric resection usually manifests as a visible ureteric orifice at the time of cystoscopy. If the distal ureter is not appropriately removed, recurrence rates can be 33% to 75% in the ureteric remnant even in the absence of positive surgical margins.[7-12] On the other hand, worsened clinical outcomes in the

Table 2. Predictors of recurrence-free survival after radical nephroureterectomy for upper tract urothelial carcinoma

Variable		*p* value	Multivariable HR	95% HR confidence limits	
DUM Method	INTRAVESICAL vs. EXTRAVESICAL	0.0002	0.628	0.492	0.801
	ENDO vs. EXTRAVESICAL	0.6440	0.916	0.633	1.327
	ENDO vs. EXTRAVESICAL	0.0424	1.488	1.014	2.185
Age		0.0003	1.022	1.010	1.034
Tumour location	Ureter vs. renal	0.9404	0.989	0.732	1.336
	Ureter and renal vs. renal only	0.0001	1.718	1.301	2.267
Laparoscopic vs. open		0.1427	1.200	0.940	1.532
pT Stage	pT2 vs. pT1	0.5245	1.111	0.803	1.536
	pT3 vs. pT1	0.2257	1.199	0.894	1.607
	pT4 vs. pT1	0.4469	1.247	0.706	2.200
High grade		0.1198	1.234	0.947	1.607
Concurrent CIS		0.5939	1.079	0.817	1.424
PSMs		0.0210	1.499	1.063	2.114
Perioperative chemotherapy		0.0003	1.897	1.338	2.689
Multifocal tumour		0.0889	1.331	0.958	1.849
Sessile architecture		0.8866	0.958	0.535	1.718
LVI		0.0591	1.412	0.987	2.021
Nodal status	N0 vs. Nx	0.9322	1.012	0.767	1.336
	N1 vs. Nx	0.0004	2.222	1.428	3.456

Hazard ratios were determined with a multivariable Cox regression analysis and reported with their 95% confidence interval and a p value less than 0.05 regarded as significant. HR: hazard ratio; ENDO: extravesical and endoscopic intravesical; DUM: distal ureter management, pT: pathological tumour; CIS: carcinoma in situ; LVI: lymphovascular invasion; PSM: positive surgical margin; EXTRAVESICAL: extravesical ureter; INTRAVESICAL: open intravesical.

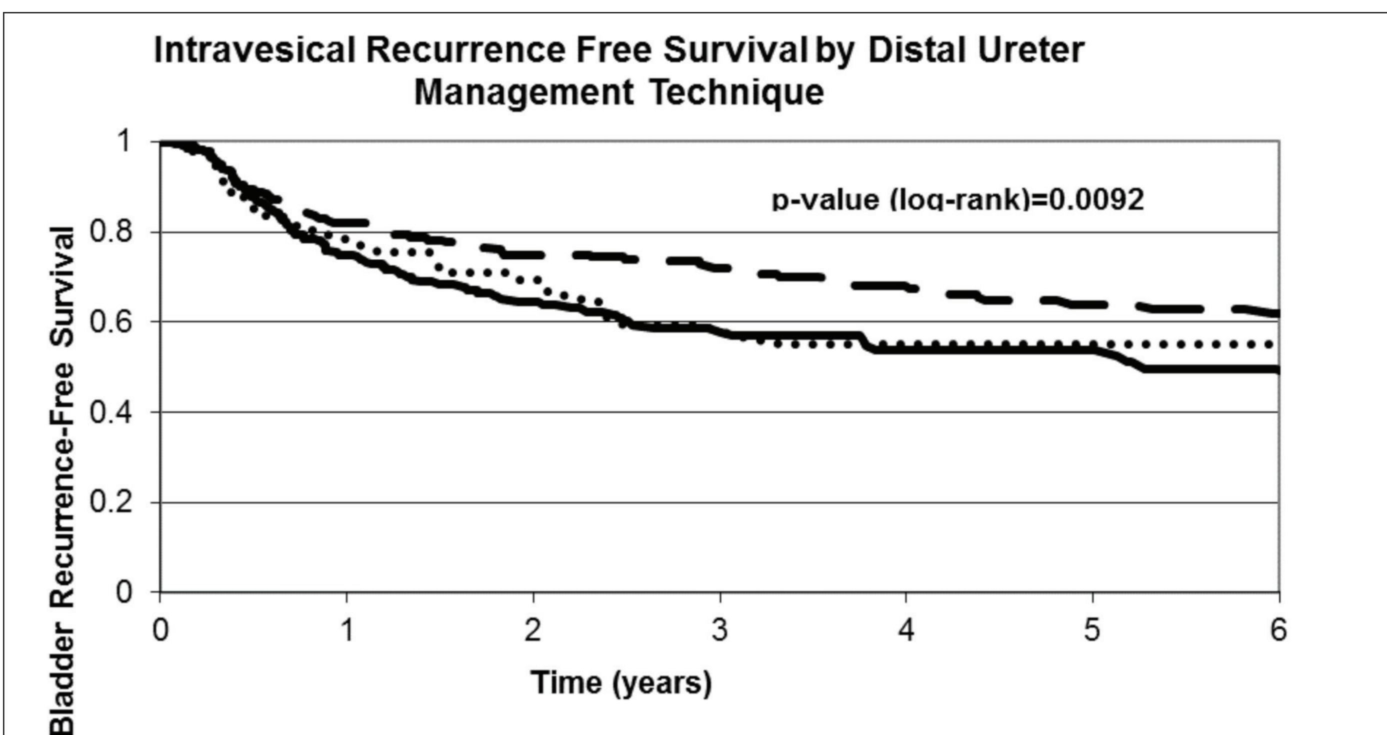

Fig. 2. Intravesical recurrence-free survival (iRFS) of patients undergoing radical nephroureterectomy over time, stratified by distal ureter management method. Survival analysis is performed with the Kaplan-Meier method using a log-rank test to evaluate for significant differences. *P* values less than 0.05 are regarded as significant. EXTRAVESICAL: extravesical ureter; INTRAVESICAL: extravesical and open intravesical; ENDOSCOPIC: extravesical and endoscopic intravesical; long dash line: INTRAVESICAL; dotted line: ENDOSCOPIC; solid line: EXTRAVESICAL.

ENDOSCOPIC group might relate to inadequate ureteral occlusion during the procedure or periureteric or perivesical seeding secondary to extravasation.

In efforts to control for confounding variables in predicting recurrence, we have performed multivariable analysis with known clinicopathologic prognosticators. Overall RFS has shown a similar trend of being highest with an INTRAVESICAL technique, found to be superior to ENDOSCOPIC and EXTRAVESICAL groups. ENDOSCOPIC and EXTRAVESICAL did not differ significantly on multivariable analysis. We have not specifically reported multivariable analysis for iRFS as this data are currently under a publication embargo and due to be reported on separately by other members of our collaboration examining another hypothesis. Nonetheless, multivariable analysis for iRFS is consistent with the univariable analysis—with a statistically higher Cox regression hazard ratio of intravesical RFS seen after radical nephroureterectomy with EXTRAVESICAL and ENDOSCOPIC techniques compared to INTRAVESICAL[18] (oral communication with Dr. J. Mauermann and Dr. W. Kassouf).

A number of prior studies have been published on this topic. The largest of these studies, published by Xylinas and colleagues,[19] is a multi-institutiona l study of 2681 patients with a median follow-up of 57.5 months. These authors had 1822 patients in their INTRAVESICAL group, 785 in their EXTRAVESICAL group and 85 in their ENDOSCOPIC group. Their techniques were similar in terms of INTRAVESICAL and EXTRAVESICAL, but they describe coagulating the ureteric orifice to prevent distal seeding during radical nephroureterectomy rather than a needlescopically applied Endoloop as generally used in our study. These authors did not find a difference in overall survival, disease-specific survival or RFS when their definition of recurrences excluded intravesical recurrences. When looking at intravesical recurrences, the iRFS for INTRAVESICAL, EXTRAVESICAL and ENDOSCOPIC, respectively, was 69%, 69% and 61% at 2 years then 58%, 51% and 42% at 5 years. This showed a statistically significant worse iRFS for ENDOSCOPIC relative to INTRAVESICAL and EXTRAVESICAL. Although EXTRAVESICAL had a lower iRFS than INTRAVESICAL, this result was not statistically significant. Multivariable Cox regression of predictors of intravesical recurrence also demonstrated that ENDOSCOPIC and EXTRAVESICAL both had higher hazards of intravesical recurrence, although only the former was significant. A subsequent study from this collaboration incorporated endoscopic management of the distal ureter as a predictor of intravesical recurrence.[20] In their multi-institutional series of 773 patients that had overlapping data with Xylinas and colleauges,[19] Walton and colleagues[21] have also found endoscopic management to result in higher risks of tumour recurrence and cancer death on multivariable analysis. Ultimately, this large series generally corroborate our findings that a cystotomy with intravesical bladder cuff excision is required to ensure that the entire intramural ureter has been resected.

Li and colleagues[22] have reported on 301 patients treated with ENDOSCOPIC (n = 91), INTRAVESICAL (n = 81), and EXTRAVESICAL (n = 129). There were no differences in baseline characteristics between groups and the groups did not differ significantly in rates of bladder recurrence, local retroperitoneal recurrence, contralateral recurrence or distant metastasis. Additionally, there were no differences in RFS and cancer-specific survival between groups. Walton and colleages[23] have also published a retrospective study comparing ENDOSCOPIC to INTRAVESICAL in 138 patients. These authors report equivalent RFS and disease-specific survival for these techniques. Groups did not significantly differ in recurrences at the resection site or elsewhere in the bladder. Likewise, in their entirely laparoscopic series of 110 patients, Allard and colleagues[24] found that ENDOSCOPIC, INTRAVESICAL, and EXTRAVESICAL groups had comparable recurrence rates. Numerous smaller non-randomized retrospective studies have been published which do not demonstrate the superiority of any one of these techniques.[25,26]

The lack of outcome differences between techniques other than those found by Xylinas and colleagues[19] may relate to the fact that other small studies would be underpowered and had limited follow-up. Additionally, large multicentered studies tend to include different techniques, which may reduce the confounding effect of an irreproducible novel technique used in a single centre. Several variations on the endoscopic approach are likely being used, including endoscopic resection of the ureteric orifice, cauterization of orifice followed by excision with a Collings knife, and laparoscopic ligation

Table 3. Sites of local recurrence stratified by method of distal ureter management

Site of recurrence	Distal ureter management				
	EXTRAVESICAL (n = 316)	INTRAVESICAL (n = 406)	ENDO (n = 98)	Total (n = 820)	*p* value
Bladder	66 (20.9%)	77 (19.9%)	23 (23.5%)	166 (20.2%)	0.57
Ureteral stump	1 (0.00%)	4 (0.01%)	0 (0%)	5 (0.01%)	0.37
Contralateral ureteric	4 (0.01%)	4 (0.01%)	0 (0%)	8 (0.01%)	0.54

EXTRAVESICAL: extravesical ureter; INTRAVESICAL: open intravesical; ENDO: extravesical and endoscopic intravesical.

of the orifice with an Endoloop followed by Collings knife excision. This is relevant because newer modifications in ENDOSCOPIC technique may allow for decreased tumour recurrence.[3,5] The precise method of ENDOSCOPIC used by many surgeons in this study was not analyzed. The possibility that individual variations on endoscopic management approaches may correlate with improved outcomes should be examined in future prospective studies.

Large variations in the rates and technical details of lymphadenectomy have been described in the literature[27,28] and accordingly lymphadenectomy was not uniformly performed in this multi-institutional series (Nx = 72.9%). Nodal metastases can serve as an independent predictor of recurrence and mortality[5] and it is unknown if the groups differed in their nodal status without lymphadenectomy. It is also not established whether lymphadenectomy itself may improve outcomes.[27]

The European Association of Urology UTUC guidelines suggest that location of UTUC and multifocality serve as predictors of poor prognosis. Ureteric tumours and multifocal tumours are thought to have worse outcomes than renal pelvic tumours or unifocal tumours.[14] Studies have been mixed on whether ureteric tumour location serves as an independent predictor of worsened prognosis.[29-33] Multifocality has been more supported as an independent marker of poor prognosis.[32-34] In this study, ureteric tumour location was not found to result in worsened RFS on multivariable analysis, although ureteric and renal pelvic tumours had a worsened RFS and there was a trend to worsened RFS with multifocal tumours on multivariable analysis. Because the distribution of tumour location and percentage of patients with multifocality did not differ significantly between groups, our assumption is that whatever selection biases are incurred by these factors are dispersed similarly among groups.

This study was also conducted before the publication of high quality evidence surrounding the use of postoperative intravesical chemotherapy to prevent intravesical recurrences.[35-37] It is unknown how the use of postoperative intravesical chemotherapy will affect these results.

This study has a number of limitations that may bias its results. These include its retrospective nature, large time period (1990-2010), lack of centralized pathologic review and heterogeneity in institutional practice patterns. Because this was an observational study, there was no systematic control on which patients received each distal ureter management technique. Additionally, even within distal ureter management groups, subtle technical variations exist that may confound the overall results.

Accordingly, some clinicopathologic parameters differed between groups. INTRAVESICAL had the lowest utilization among female patients and may relate to real or perceived cosmetic concerns about an additional incision. ENDOSCOPIC was more commonly utilized with laparoscopic radical nephroureterectomy compared to EXTRAVESICAL and INTRAVESICAL, a trend likely attributable to minimally invasive surgeons being more likely to employ both techniques. ENDOSCOPIC methods were less likely to be employed in the presence of carcinoma in situ possibly due to concerns of perivesical seeding. Pathologic tumour stage when analyzed as a whole also differed between groups—but we felt that this was an artifact of having low numbers in some pT stages rather than a real clinically significant difference.

Although INTRAVESICAL may be associated with improved oncologic outcomes, we did not have the data to evaluate the morbidity of INTRAVESICAL. INTRAVESICAL may necessitate an additional incision, added operative time and a more extensive dissection. It is unknown how these requirements affect meaningful outcomes, such as post-procedural complications, cost, and quality of life. A patient's life expectancy, compliance with surveillance for intravesical recurrence, and risk for postoperative complications are thus important considerations in choosing a distal ureter management technique.

Median follow-up for all patients was 24.6 months in this study. Margulis and colleagues have previously reported median times to all-cause mortality and cancer-specific mortality at 24.0 and 18.5 months, respectively, after radical nephroureterectomy.[5] Due to limited follow-up, overall survival and cancer-specific survival for each technique have not been reported. On the other hand, median time to tumour recurrence has previously been found to be 10.4 months,[5] which is similar to this study.

Conclusion

Open intravesical excision of the distal ureter and bladder cuff (INTRAVESICAL) during radical nephroureterectomy for upper urinary tract urothelial carcinoma was associated with improved overall and intravesical recurrence free survival compared with EXTRAVESICAL and ENDOSCOPIC approaches. These findings suggest that INTRAVESICAL should be considered the gold standard approach for distal ureter management during radical nephroureterectomy with respect to preventing tumour recurrence. While an intravesical technique may provide the best oncologic outcomes, a patient's life expectancy, compliance with surveillance for intravesical recurrence, and risk for postoperative complications are also important considerations in choosing a technique.

Competing interests: Dr. Kapoor, Dr. Dason, Dr. Allard, Dr. Shayegan, Dr. Lacombe, Dr. Rendon, Dr. Jacobsen, Dr. Fairey, Dr. Izawa, Dr. Black, Dr. Tanguay, Dr. Chin, Dr. So, Dr. Lattouf, Dr. Bell, Dr. Saad, Dr. Drachenberg, Dr. Cagiannos, Dr. Fradet, Dr. Alamri and Dr. Kassouf all declare no competing financial or personal interests.

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