Année 2020/2021
N°

Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État

par

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Née le 29/07/1990 à Limoges (87)

TITRE :

Développement et évaluation du « PNUT pentafecta » pour les patients atteints d'un carcinome urothélial des voies excrétrices de haut risque traités par néphro-urétérectomie totale

Présentée et soutenue publiquement le **29/10/2021** date devant un jury composé de :

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

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List of acronyms

ASA score: American Society of Anesthesia
BMI: Body Mass Index
Cis: Carcinoma In Situ
CT: computered tomodensitometry
EAU: European Association of Urology
ECOG: Eastern Cooperative Oncology Group
IQR: Inter Quartile Range
Mos: Months
NUT: néphro-uréterectomie totale
OR: Operating Room
OS: Overall survival
PV: pentafecta validated
PNV: pentafecta not validated
PNUT: Pentafecta NUT
RFS: Recurrence-Free Survival
RNU: Radical Nephro-Ureterectomy
SD: Standard Deviation
URS: Uretero-Renoscopy
UTUC: Upper Tract Urothelial Carcinoma
YAU: Young academic Urologists

Résumé

Contexte :
De nombreux outils ont été développés ces dernières années en onco-urologie avec pour but l'évaluation et l'optimisation de la prise en charge du patient. Pour la néphro-urétérectomie totale (NUT) qui est le traitement de référence des tumeurs des voies excrétrices supérieures (TVES) de haut risque (HR), aucun outil d'évaluation n'a encore été proposé. Le but de cette étude était de proposer un pentafecta afin d'évaluer la qualité de la prise en charge chirurgicale des patients traités par NUT pour une TVES- HR .

Matériel et méthodes :
Il s'agit d'une étude rétrospective, multicentrique dans laquelle l'ensemble des patients atteints de TVES-HR et traités par NUT dans trois centres universitaires français entre 1998 et 2020 ont été inclus dans une base de données commune. Les patients avec un suivi de moins de 12 mois, de bas risque (critères EAU 2020) ou présentant trop de données manquantes étaient exclus. Après analyse systématique de la littérature, un consensus entre les membres d'un groupe d'experts internationaux (YAU urothelial carcinoma working group) a été réalisé pour valider le pentafecta (PNUT). Les critères validant le pentafecta étaient : absence de complication hématologique (transfusion périopératoire, évènement thromboembolique), absence de complication majeure (Clavien Dindo ≥3) dans les 3 mois, réalisation d'une collerette vésicale, absence de marge chirurgicale et absence récidive dans l'année suivant la NUT. Nous avons ensuite défini deux groupes de patients selon la validation du pentafecta, et évalué son impact sur les résultats oncologiques.

Résultats :
Parmi les 387 patients de la cohorte, 237 répondaient aux critères d'inclusion dont 67 (28%) présentaient un pentafecta validé (PV). Les caractéristiques préopératoires entre les groupes étaient similaires. Avec un suivi médian de 51 mois, la survie globale à 5 ans était supérieure chez les patients présentant un PV 80.5% (IC95% 70.7-91.7) vs 46.5% (IC95% : 38.3-56.5) pour PNV. De la même manière, la survie sans récidive à 5 ans était de 76.1% (IC 95% : 65.3-88.6) vs 50.4% (IC95% : 41.8-60.7) dans les groups PV et PNV respectivement ($p< 0.0001$), on observait également une meilleure survie sans métastase à 5 ans ($p<0.05$). Nous n'avons pas retrouvé dans notre population de facteurs prédictifs préopératoires d'échec du pentafecta (tous les $p> 0,05$).

Conclusion :

Le pentafecta que nous avons proposé a montré que sa validation avait un impact statistiquement significatif sur les résultats oncologiques à long terme pour la survie sans récidive et la survie globale. Il pourrait être utilisé à l'avenir pour évaluer la prise en charge des patients atteints de TVES-HR. Néanmoins, une validation externe sur une plus grande population reste nécessaire pour confirmer son applicabilité.

Mots clés : Néphro-urétérectomie totale, carcinome urothélial des voies excrétrices supérieures, pentafecta

Abstract

Context:
Many tools have been developed in recent years in onco-urology with the aim of evaluating and optimizing patient management. For Radical nephro-ureterectomy (RNU), which is the reference treatment for high-risk (HR) upper tract urothelial carcinoma (UTUC), no assessment tool has yet been proposed. The aim of this study was to propose a pentafecta to assess the quality of surgical management of patients treated with RNU for high-risk UTUC (HR-UTUC).

Materials and Methods:
This was a retrospective, multicenter study in which all patients with HR-UTUC Patients with a follow-up of less than 12 months, low risk (EAU 2020 criterion) or with too much missing data were excluded. After a systematic review of the literature, a consensus among members of an international expert group (YAU urothelial carcinoma working group) was reached to validate the pentafecta (PNUT). The criteria validating the pentafecta were: absence of hematological complication (perioperative transfusion, thromboembolic event), absence of major complication (Clavien Dindo ≥3) within 3 months, realization of a bladder cuff, absence of surgical margin and absence of recurrence within one year after the RNU. We then defined two groups of patients according to the validation of pentafecta and evaluated its impact on oncological outcomes.

Results:
Of the 387 patients in the cohort, 237 met the inclusion criteria, of which 67 (28%) had a validated pentafecta (PV). Preoperative characteristics between groups were similar. With a median follow-up of 51 months, the 5-year overall survival was superior in patients with PV 80.5% (CI95% 70.7-91.7) vs 46.5% (CI95%: 38.3-56.5) for PNV. Similarly, the 5-year recurrence-free survival was 76.1% (95% CI: 65.3-88.6) vs 50.4% (95% CI: 41.8-60.7) in the PV and PNV groups respectively ($p<0.0001$), and there was also a better 5-year metastasis-free survival ($p<0.05$). We did not find in our population any predictive factors of pentafecta failure (all $p> 0.05$).

Conclusion:
Our proposed pentafecta has been shown to have a statistically significant impact on long-term oncologic outcomes for recurrence-free survival and overall survival through validation. It could be used in the future to evaluate the management of patients with HR-STV. Nevertheless, external validation in a larger population is still needed to confirm its applicability.

Key words: Radical nephro-ureterectomy, upper-tract urothelial carcinoma, pentafecta

Introduction

Upper-Tract Urothelial Carcinoma: epidemiology and management

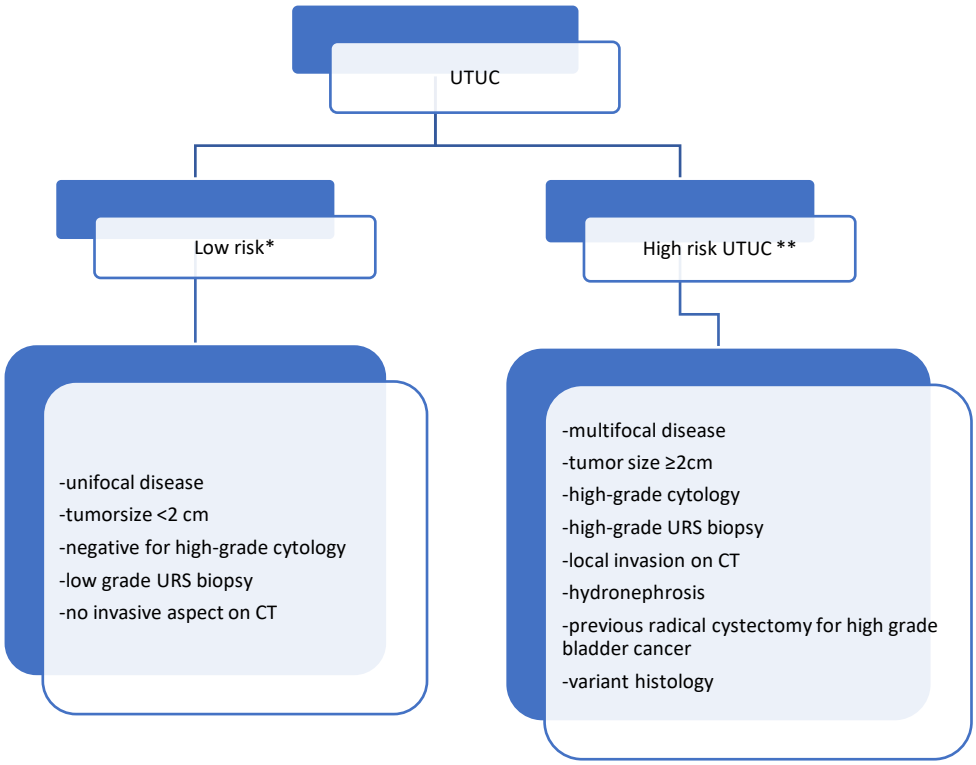
Upper tract urothelial carcinoma (UTUC) is considered as a rare disease accounting for less than 10% of all the urothelial carcinomas (1,2), its incidence is estimated around 2 per 100 000 inhabitants in western countries, increasing in recent years probably related to increased surveillance of patients with a history of bladder tumor(3,4) with a peak incidence in elderly men between 70-90 years of age.(5–7)

It has one of the poorest prognoses among uro-oncologic malignancies, mainly due to its late diagnosis at an invasive tumor stage. Indeed, approximately two-thirds of the patients present with locally advanced disease, and 7% with primary metastasis(3,8,9). It presents a relatively high recurrence rate (>30% at 5 years). The 5-year cancer specific survival (CSS) of advanced UTUC is <50% for tumors ≥pT2 and <10% for those with pT4 stage(10–12).

UTUC may affect the entire urothelium between the renal cavities and the ureteral ending. It is most often pyelocaliceal (40%) and less often ureteral or multifocal (1). The diagnosis is frequently incidental diagnosed on tomodensitometry exam, but can also be symptomatic (renal colic, hematuria) which is more likely to occur at an advanced stage of the disease.

Patients with localized UTUC are stratified in high or low risk of progression and recurrence thanks to pre-operative prognostics variables (1,13,14) ***Figure 1 et 2***. Initially used in patients with imperative indications such as multiple comorbidities, impaired renal function, solitary kidneys, or bilateral tumors, approaches using endoscopic kidney-sparing surgery (KSS) or segmental ureterectomy have become an accepted curative alternative in patients with low-risk features(15). High-risk disease is defined as having any of the following characteristics: hydronephrosis, tumor size more than 2 cm, high-grade cytology, high-grade biopsy, multifocal disease, previous radical cystectomy for bladder cancer and variant histology(1).

Radical nephroureterectomy (RNU) with bladder cuff excision, with or without lymph node dissection, is the standard of care for high-risk UTUC for non-metastatic patients (1,16,17).



CT= computed tomography; URS = ureteroscopy; UTUC= upper urinary tract urothelial carcinoma
*all these factors need to be present
**any of these factors need to be present

Figure 1: Patients risk stratification for Upper Tract Urothelial Carcinoma based on pre-therapeutic criteria.

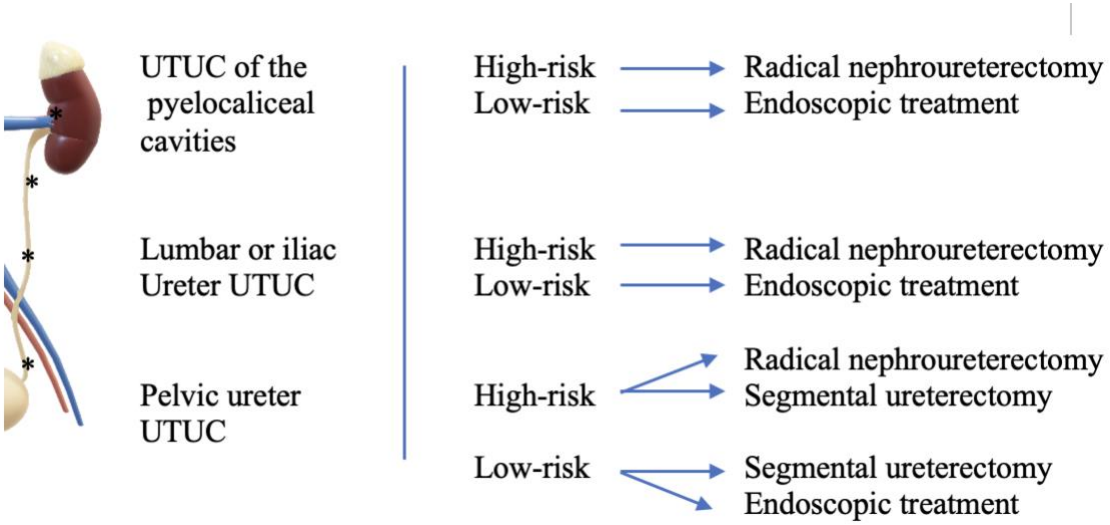


Figure 2: Therapeutic strategy based on risk-stratification

Rational

In the last decade, the management of patients with high risk UTUC has been highly investigated. Indeed, not only the diagnostic step with improvement in imaging(3), but also the surgery itself (implementation of bladder cuff excision (18,19), impact of surgical approach, role of lymph node dissection (20,21)) as well as the perioperative systemic therapy have been debated and improved (1,15,18,19,21–24). In addition, several predictive tools have been developed for the management of UTUC(12,13,25–28) refining patient selection criteria to improve precision medicine and thus patient care.

Lately several trifecta/pentafecta tools have been described and used for partial nephrectomy, radical prostatectomy or cystectomy (27,29,30). These tools are composite criteria including perioperative and oncological data to assess the quality of patient's management and have proven their positive impact in increasing overall and specific survival while being a good reflection of surgeon learning curve (27,30,31). Nevertheless, due to the rarity of the disease and the lack of high-volume/expert center labialization, no precise tool has been developed to assess the management of high-risk UTUC treated by RNU. But in the contemporary health-care evaluation system where standardizing outcomes report as well as monitoring and accredit surgical management become mandatory, these tolls are highly needed. Therefore, in this study, we aimed to establish a pentafecta assessing the management of patients with high-risk UTUC treated by RNU.

Material and Methods

Study population

We performed a retrospective analysis of patients who underwent RNU for intent to cure UTUC from three French academic hospital centers (Rennes, Tours and Toulouse) from January 1990 to January 2020. Were included all patients over 18 years-old treated by RNU for a non-metastatic HR-UTUC according to the EAU guidelines (European Association of Urology). Patients with non-urothelial carcinoma (renal cell carcinoma (n= 11 patients), other (n= 6) and no tumor founded (n=6)), patients with other surgery than RNU (n= 13), patients with EAU low-risk criteria (n= 58), patients with no follow-up available (n= 38) or with missing data (n= 18) were excluded. Patient information were collected on the same pre-defined dataset and all information were anonymized prior to datasharing.

Among the baseline patients' characteristics, were recorded: the age at the diagnosis, gender, ASA score, ECOG score, BMI (Body mass Index) index, smoking status (current smokers, former and non-smokers), preoperative renal function, history of diabetes, hypertension, or previous lung disease, history of bladder cancer. The preoperative imaging data with CT stage was also included when available.

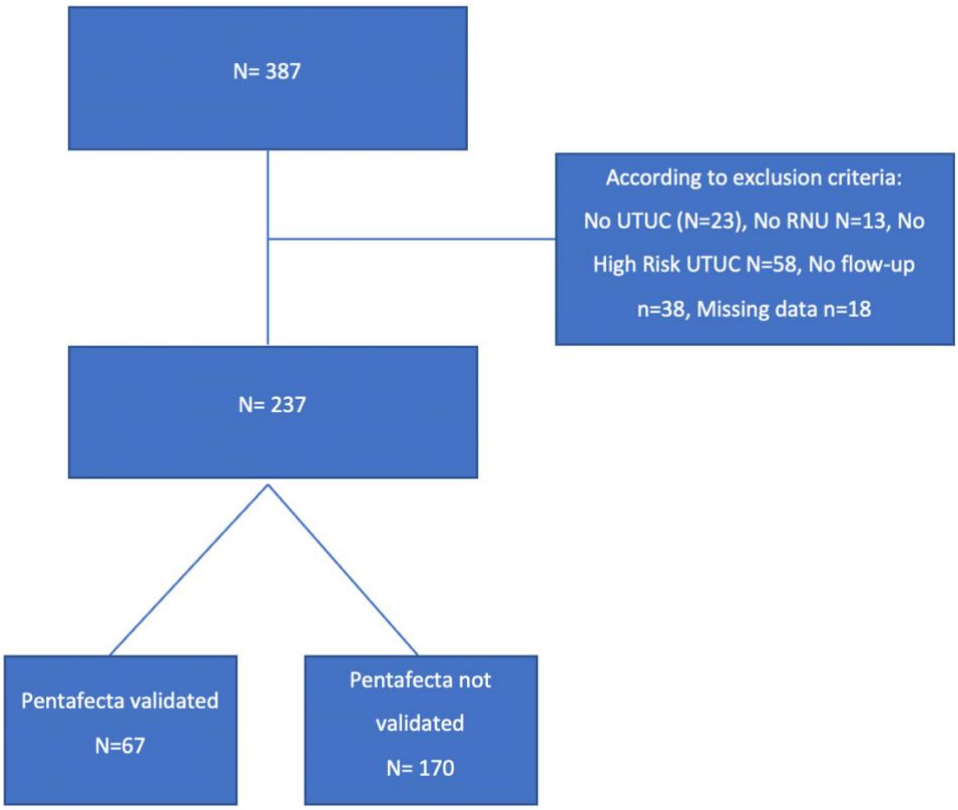


Figure 3: Flow chart

Definition of the PNUT Pentafecta

After a systematic review of the literature, a consensus among members of an international group of young academics experts (YAU urothelial carcinoma working group) was reached to validate a pentafecta (*PNUT project(Pentafecta for Nephro Ureterectomy Tool)*)(27,30–34). This pentafecta, included:

Three perioperative criteria (34–37):

1. The performance of a monobloc bladder-cuff excision
2. The absence of hematological complications. Defined by need for blood transfusion or the occurrence of a thromboembolic event such as pulmonary embolism or deep vein thrombosis
3. The absence of major complication within 3 months postoperatively

Two oncological criteria:

4. The absence of positive surgical margin (either in the soft tissue or in the ureter) on final specimen analysis
5. The absence of recurrence of any type (local, contralateral, distant or bladder recurrence) at 12 months.

If a patient had simultaneously reached these 5 criteria he was considered as pentafecta-validated (PV).

Management and follow-up

After preoperative evaluation with at least a CT-scan imaging and a ureteroscopy when indicated, patients were classified at high-risk of UTUC and RNU was planned. The decision to perform the RNU by open or laparoscopic approach with or without robotic assistance, as well as the decision to perform lymphadenectomy and its extent was lead to the surgeon discretion based on patient and preoperative disease characteristics following standard templates previously described(20,38,39).

Perioperative data included the type of surgery, length of procedure, estimated blood loss and the likely need for transfusion, the lymph node dissection.

The use of early postoperative endovesical instillation of chemotherapy was also recorded.

Post-operative data included: the length of stay, the prevalence of major (≥III) and minor (≤II) complications according to the Clavien-Dindo classification (40) within 3 months from surgery.

All surgical specimens were exanimated by a local dedicated uro-pathologists. Tumor grade was determined according to the 2016 World Health Organization (WHO) classification (41). Tumor stage was evaluated using the 2002 Union for International Cancer Control tumor, node, metastasis classification system (TNM) (cf annexes).

Regarding the oncological outcomes, we assessed the anatomopathological stage and grade pTNM (41,42), the presence of positive surgical margins on the ureter or soft tissues, the occurrence of a local, contralateral, distant or intravesical recurrence, adjuvant chemotherapy or radiotherapy. Recurrence-free survival (RFS) was defined by any local or distant recurrence and metastasis but not bladder recurrence. For the overall survival (OS) analysis, we calculated the interval from RNU to death. Patients were censored at their last follow-up. The follow-up was set up according to the habits of each center, guided by international recommendations (1) with regular imaging every 6 months initially and cystoscopy every three or six months initially then annually.

Outcomes of interest

The primary outcome of the present study was to assess the PNUT rate and its impact when validated (PV) on oncological outcomes. The secondary outcome was to research predictors of pentafecta failure in order to help the clinicians to anticipate and adapt their therapeutic strategy.

Statistical analysis

Report of the collected categorical variables included frequencies and proportions in percent. Reports of the collected continuous variables focused on means, medians, and interquartile ranges (IQR). Normality of continuous variables was tested by the Kolmogorov-Smirnov normality test. The equality of variances was tested by the F-test. With respect to Pentafecta status, comparisons were performed using the Fisher's exact test, Wilcoxon rank sum test and Pearson's Chi-squared test as appropriate.

Logistic regression was performed to identify risk factors for pentafecta failure (PNV). Recurrence-free survival (RFS), and overall survival (OS) were graphically visualized using the Kaplan-Meier method. The difference between groups was assessed using a log-rank test. Multivariable Cox regression models were adjusted for cofounder's survival outcomes to investigate the association of PV with RFS, CSS, and OS. Association between clinicopathological parameters and OS, RFS and CSS was assessed in univariable and multivariable models using Cox hazards regression model.

All statistical analyses were performed using R Version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, 2020) and pValue.io. The statistical significance level was set at $p<0.05$.

Results

Patients characteristics.

Among 387 patients in the multicentric cohort, 237 patients were included after the exclusion criteria have been applied. Among them, 67 patients (28%) validated the pentafecta (PV) proposed (no hematologic complication and no major complication within 3 months and bladder cuff excision and no positive margin and no recurrence within 12 months) ***(Figure 3)*** and were compared to the rest of the cohort (PNV).

Patients' characteristics are presented in ***Table 1***. There was no statistical difference between both groups regarding BMI, ASA score, renal function, diabetes and hypertension. There was more patients with a lower ECOG score (p=0.05) in the PNV group. In the overall cohort, the median age was 68 (60,77). There was a high proportion of men (73%; n=174) in our population but the distribution was similar between groups (p=0.09).

	Total cohort	PNUT Pentafecta validated		
Characteristic	N = 237	no, N = 170	yes, N = 67	p-value
Age	68 (60, 77)	69 (60, 78)	67 (59, 75)	0.08
Gender				0.09
male	174 (73%)	130 (76%)	44 (66%)	
female	63 (27%)	40 (24%)	23 (34%)	
ASA				**0.01**
0	1 (0.4%)	0 (0%)	1 (1.5%)	
1	29 (12%)	15 (8.8%)	14 (21%)	
2	130 (55%)	92 (54%)	38 (57%)	
3	73 (31%)	59 (35%)	14 (21%)	
4	4 (1.7%)	4 (2.4%)	0 (0%)	
BMI	25.0 (22.5, 27.9)	24.9 (22.2, 27.6)	26.0 (23.0, 28.0)	0.4
Unknown	38	21	17	
ECOG				**0.03**

0	140 (68%)	93 (64%)	47 (78%)	
1	50 (24%)	42 (29%)	8 (13%)	
2	15 (7.3%)	11 (7.5%)	4 (6.7%)	
3	1 (0.5%)	0 (0%)	1 (1.7%)	
Unknown	31	24	7	
Smoking_status				0.5
Never	57 (27%)	45 (29%)	12 (21%)	
Former	82 (38%)	59 (38%)	23 (40%)	
Current	75 (35%)	52 (33%)	23 (40%)	
Unknown	23	14	9	
Hypertension	102 (43%)	77 (45%)	25 (37%)	0.3
Diabetus	35 (15%)	26 (15%)	9 (13%)	0.7
Preoperative creatinin level	100 (79, 129)	104 (79, 132)	95 (80, 122)	0.4
Unknown	20	12	8	
Neoadjuvant chemotherapy	4 (1.7%)	3 (1.8%)	1 (1.5%)	>0.9
Preoperative ureteroscopy	131 (55%)	96 (56%)	35 (52%)	0.6
Clinical CT stage				0.1
cT0	16 (18%)	12 (17%)	4 (18%)	
cTa/cT1	24 (26%)	15 (22%)	9 (41%)	
cT2	19 (21%)	13 (19%)	6 (27%)	
cT3	24 (26%)	22 (32%)	2 (9.1%)	
cT4	8 (8.8%)	7 (10%)	1 (4.5%)	
Unknown	146	101	45	
Lymph node status on CT				0.8
No	197 (90%)	140 (91%)	57 (89%)	
Lymphnodes < 1cm	21 (9.6%)	14 (9.1%)	7 (11%)	
Lymphnodes > 1cm	19 (8%)	16 (9%)	3 (4.5%)	
Hydronephrosis on CT	157 (66%)	112 (66%)	45 (67%)	0.9
History of bladder cancer	67 (28%)	53 (31%)	14 (21%)	0.1
Median (IQR); n (%)				
Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test				

CT: computered tomodensitometry, ASA score: American association of anesthesia; BMI: body mass index;

Table 1: Patients' characteristics in the overall population and according to the validation of the pentafecta

Perioperative outcomes

The mean operative time was similar between groups (p= 0.32). The surgical approach was similarly distributed. The hospital length of stay was shorter in the PV compared to the PNV (7.9 vs. 10.6 days; p<0,001) ***Table 2***. Besides major complication, there were also fewer minor complications (Clavien-Dindo I-II) in the PV group (16% vs. 24.7%; p=0.04). In the PNV group there was 20.8% of major complication. A total of 28 (12%) patients required perioperative blood transfusions and postoperative thromboembolic disease was reported in only two patients.

	Total cohort	PNUT Pentafecta validated		
Characteristic	N = 237	no, N = 170	yes, N = 67	p-value
Type of surgery				**0.03**
RNU with bladder cuff	222 (94%)	155 (91%)	67 (100%)	
RNU without cuff	11 (4.6%)	11 (6.5%)	0 (0%)	
Nephrectomy without ureterectomy	4 (1.7%)	4 (2.4%)	0 (0%)	
Surgical technique				0.3
Open	63 (27%)	48 (28%)	15 (22%)	
Laparoscopic	23 (9.7%)	17 (10%)	6 (9.0%)	
Robotic	50 (21%)	39 (23%)	11 (16%)	
Combination	101 (43%)	66 (39%)	35 (52%)	
side				0.06
Left	123 (52%)	94 (55%)	29 (43%)	
Right	113 (48%)	76 (45%)	37 (55%)	
bilateral	1 (0.4%)	0 (0%)	1 (1.5%)	
Monobloc cuff	219 (92%)	152 (89%)	67 (100%)	0.006
Transfusion	28 (12%)	28 (16%)	0 (0%)	**<0.001**
OR duration	240 (180, 300)	240 (180, 300)	225 (178, 300)	0.3
Unknown	69	45	24	
Lymph node dissection	67 (29%)	44 (26%)	23 (34%)	0.2
Unknown	3	3	0	
Postoperative instillation	13 (5.5%)	8 (4.7%)	5 (7.5%)	0.5
Complications	79 (33%)	70 (41%)	9 (13%)	**<0.001**
Unknown	1	1	0	
Total of major complications (≥Clavien-Dindo 3) (n)				**<0.001**
0	201 (85%)	134 (79%)	67 (100%)	
1	35 (15%)	35 (21%)	0 (0%)	
3	1 (0.4%)	1 (0.6%)	0 (0%)	

Highest minor complication Clavien-grade				
1	21 (8.8%)	14 (8.2%)	7 (10%)	**0.046**
2	35 (15%)	28 (16%)	3 (4.5%)	
Highest major complication Clavien-grade				**<0.001**
3	21 (8.9%)	21 (12%)	0 (0%)	
4	9 (3.8%)	9 (5.3%)	0 (0%)	
5	6 (2.5%)	6 (3.5%)	0 (0%)	
Post operative creatinin level	116 (95, 136)	116 (96, 136)	116 (95, 132)	0.6
Unknown	20	11	9	
n (%); Median (IQR) OR: Operating room				
Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test				

table 2 Perioperative outcomes according to pentafecta

PNUT Pentafecta validation

Only 67 patients (28%) from our cohort reached the pentafecta with a similar PV rate between centers (p>0.05).

Validation rate of each criteria are shown in ***Figure 4 and 5***. The absence of hematological complications, i.e., the absence of the requirement for peri-operative transfusion and the absence of thromboembolic complications was accomplished for 193 patients (81%) of all our population. The absence of major complication within 3 months was achieved for 158 patients (67%).

We had negative surgical margins for 211 patients (89%) and a monobloc bladder cuff was done for 219 (92%) of all our population (237 patients). In the end the most discriminating criteria was as expected the absence of any type of recurrence including bladder recurrence at 12 months, which was achieved only for 54% (127 patients) in our population.

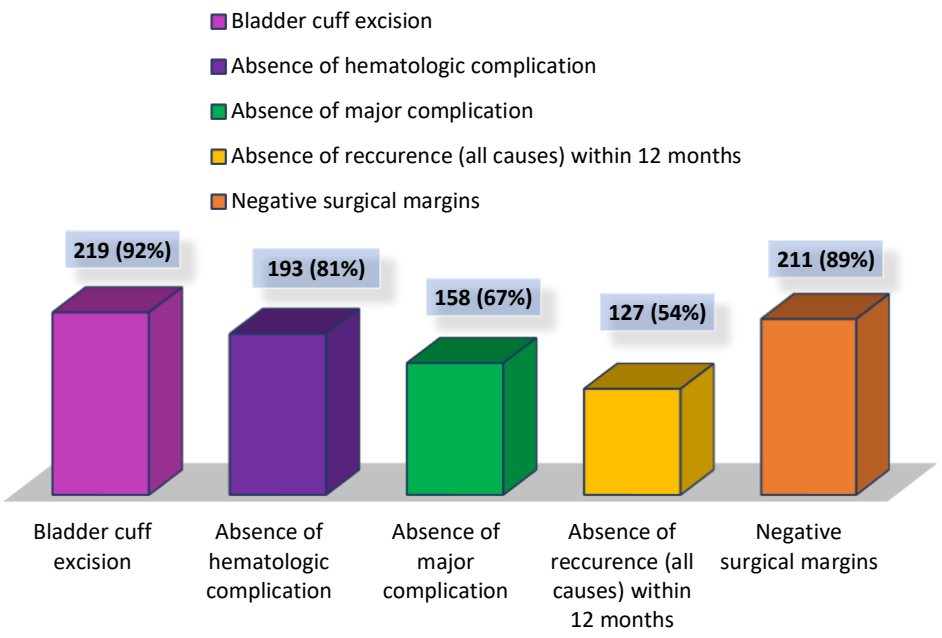


Figure 4 Validation rate of each criteria of the PV in overall population

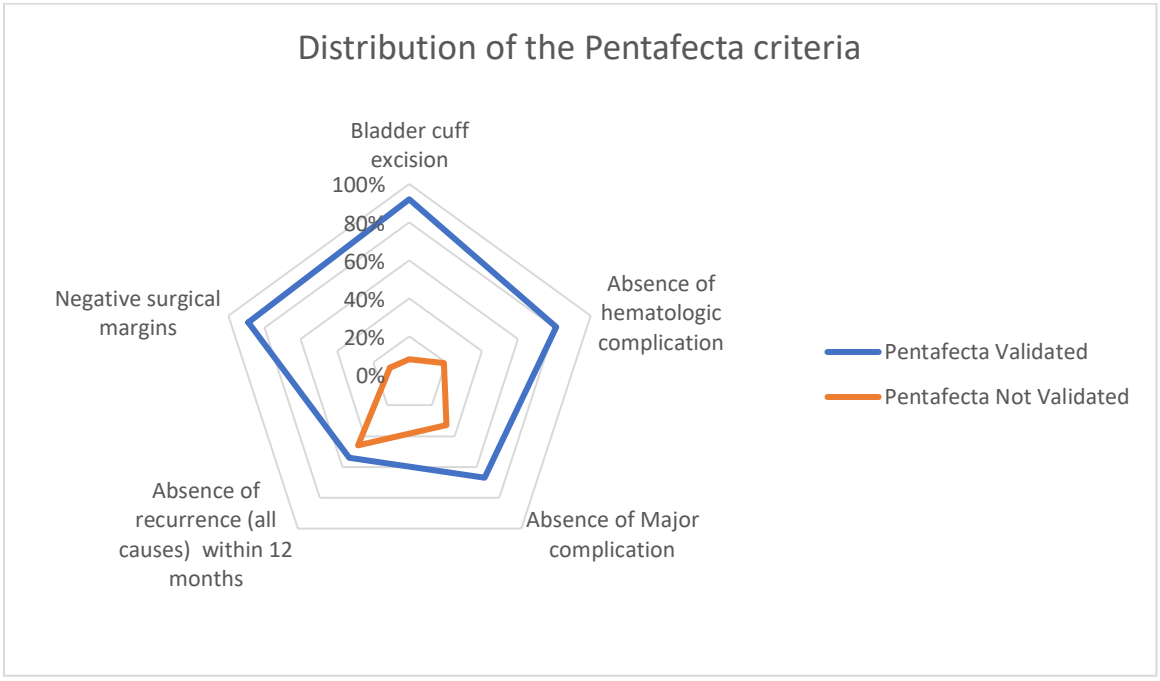


Figure 5 Distribution of the pentafecta criteria

Pathologic outcomes:

There was no difference in terms of pathological stage or CIS between groups. Nevertheless, there were more positive lymph nodes and multifocality in the PNV group (all p<0.05). The rate of positive surgical margins in the PNV group were 7.2% in soft tissue and 8.4% in the ureter.

Pathological data are summarized in ***Table 3***.

	Total cohort	PNUT Pentafecta validated		
Characteristic	N = 237	no, N = 170	yes, N = 67	p-value
Pathological stage				0.6
pT0	7 (3.1%)	6 (3.7%)	1 (1.6%)	
pTa	66 (29%)	43 (27%)	23 (37%)	
pT1	55 (25%)	43 (27%)	12 (19%)	
pT2	30 (13%)	22 (14%)	8 (13%)	
pT3	59 (26%)	41 (25%)	18 (29%)	
pT4	7 (3.1%)	6 (3.7%)	1 (1.6%)	
Unknown	13	9	4	
Pathological tumor grade				0.07
Low grade	62 (26%)	39 (23%)	23 (34%)	
High grade	175 (74%)	131 (77%)	44 (66%)	
Multifocal urothelial carcinoma	95 (40%)	77 (45%)	18 (27%)	**0.009**
Lymph node involvement				**0.01**
no	72 (31%)	43 (25%)	29 (43%)	
yes	28 (12%)	24 (14%)	4 (6.0%)	
Nx	136 (58%)	102 (60%)	34 (51%)	
Unknown	1	1	0	
Lymphovascular invasion	73 (31%)	60 (35%)	13 (19%)	**0.02**
Concomitant Carcinoma in situ	58 (24%)	47 (28%)	11 (16%)	0.07
n (%)				
Fisher's exact test; Pearson's Chi-squared test				

Table 3 Pathological characteristics

Oncological Outcomes

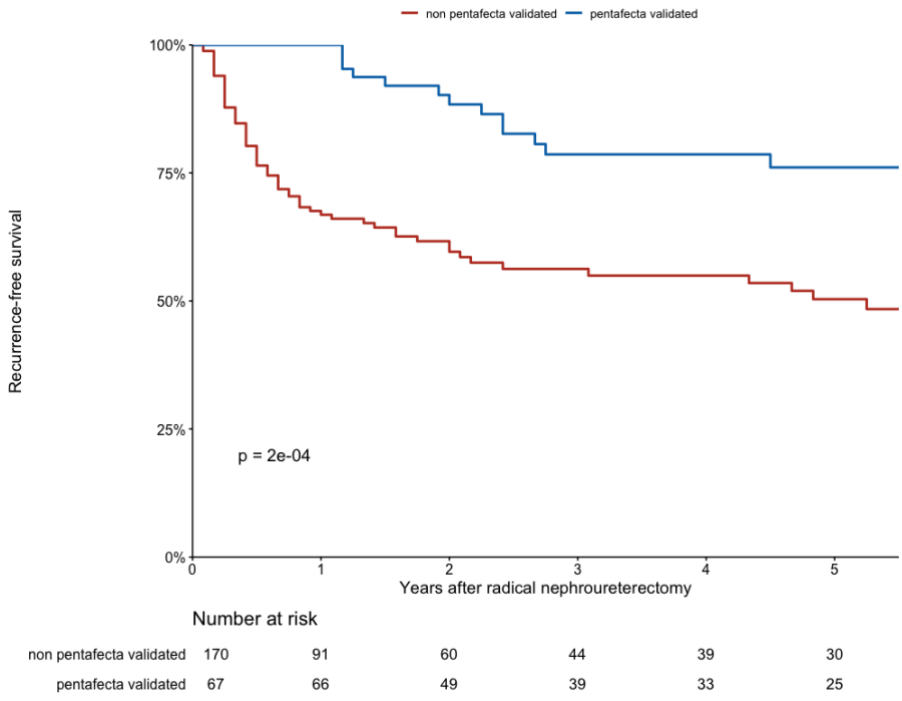
One of the co-primary endpoints was to assess the impact of PV on oncological survival. Overall, the median follow-up was 51 months (20 - 79), and 56 months (26-92) in the PV and 22.5 months (10-56)) in the PNV group (p< 0,001).

Only four patients received neoadjuvant chemotherapy without difference between groups and 32 (14%) received adjuvant chemotherapy in the PNV and PV group (16% vs. 7.5%; p=0.09).

Eighty-six patients (36,2%) experienced local or metastatic recurrence with a distribution of 41% (n= 70) vs 24% (16%) in the groups PNV and PV respectively (p= 0.013).

Preferred metastatic sites were mainly lymph nodes, bone and lung, it occurred for 37% vs 16% in the PNV and PV group respectively (p= 0.076).

The 5-year RFS estimates were 76.1 % (95% CI: 65.3 – 88.6) for PV and 50.4 % (95% CI: 41.8 – 60.7) for PNV. The 5-year OS estimates were 80.5 % (95% CI: 70.7 – 91.7) for PV and 46.5 % (95% CI: 38.3 – 56.5) for PNV. RFS and OS were significantly higher in the PV group on the Kaplan-Meir survival curves (all p<0.001) (Figure 7 A and B).



7A

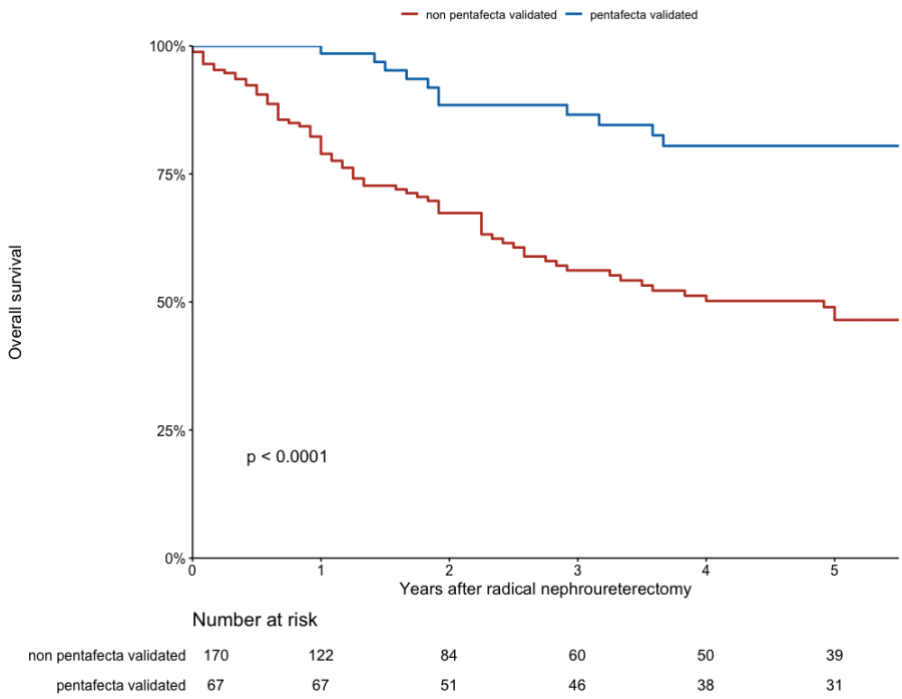


Figure 6 Kaplan Meier Curves pairwise log rank test and 5-year survival analysis. 7A: Recurrence free Survival at 5 years 7B: Overall survival at 5 years by pentafecta validated

In univariable Cox regression analysis, PV was associated with RFS and OS (HR: 0.37, 95% CI: 0.21 - 0.64; p<0.001 and HR: 0.33, 95% CI: 0.19 - 0.57; p<0.001 respectively). In the multivariable Cox regression analysis that was adjusted for age, gender, ASA, neoadjuvant chemotherapy, pathological stage, multifocality, lymph node involvement and invasion, surgical margin, postoperative instillation, adjuvant chemotherapy and radiotherapy, PV was associated with better RFS (HR: 0.38, 95% CI: 0.20 - 0.69; p<0.001) and OS (OS: HR: 0.42, 95% CI: 0.23 - 0.79; p<0.001).

	Recurrence-free Survival			Overall survival		
Characteristic	HR	95% CI	p-value	HR	95% CI	p-value
pentafecta_validated						
no	—	—		—	—	
yes	0.38	0.20, 0.69	0.002	0.42	0.23, 0.79	**0.006**
Age	1.02	1.00, 1.04	0.085	0.99	0.97, 1.01	0.3
Gender						
male	—	—		—	—	
female	1.10	0.65, 1.85	0.7	1.23	0.73, 2.09	0.4
ASA	0.92	0.61, 1.40	0.7	1.18	0.79, 1.74	0.4
Neodajuvant chemotherapy						
No	—	—		—	—	
Yes	0.49	0.07, 3.68	0.5	0.39	0.05, 2.96	0.4
Pathological Stage						
pT0	—	—		—	—	
pTa	1.30	0.16, 10.4	0.8	0.63	0.17, 2.29	0.5
pT1	5.44	0.70, 42.2	0.1	1.27	0.35, 4.60	0.7
pT2	2.99	0.36, 24.7	0.3	0.64	0.16, 2.61	0.5
pT3	5.11	0.64, 40.5	0.1	0.76	0.20, 2.88	0.7
pT4	4.04	0.41, 39.9	0.2	0.24	0.04, 1.46	0.1
multifocal						
no	—	—		—	—	
yes	0.61	0.36, 1.01	0.06	1.51	0.94, 2.43	0.09
Lymph node involvement						
no	—	—		—	—	
yes	1.36	0.62, 2.95	0.4	1.01	0.47, 2.18	>0.9
Nx	1.10	0.64, 1.91	0.7	0.87	0.51, 1.49	0.6
Lymphovascular invasion						
no	—	—		—	—	
yes	1.12	0.61, 2.05	0.7	1.59	0.85, 2.98	0.2
Surgical margin						
no	—	—		—	—	
yes	1.05	0.52, 2.14	0.9	0.95	0.49, 1.84	0.9
Postoperative instillation	0.38	0.12, 1.25	0.1	0.13	0.02, 0.95	**0.04**
Received adjuvant chemotherapy	3.06	1.68, 5.56	<0.001	2.64	1.44, 4.86	**0.002**
Received adjuvant radiotherapy	1.08	0.43, 2.72	0.9	0.65	0.26, 1.66	0.4
HR = Hazard Ratio, CI = Confidence Interval						

table 4 Multivariable Cox regression Analysis for overall survival and recurrence free survival

Secondary objective

Our secondary objective was to explore if some perioperative and intraoperative factors could predict the pentafecta failure. We performed an univariable logistic regression analysis and found that only ASA score was significant (OR: 0.47, 0.30-0.73; p< 0.001) among the patients baseline characteristics for the prediction of PNV. In a multivariable log regression no one of the preoperative variable were predictor of PNV (all p>0.05).

Characteristic	OR	95% CI	p-value
Age	1.08	0.97, 1.24	0.2
Gender			
male	—	—	
female	0.50	0.00, 20.0	0.7
ASA	0.02	0.00, 1.01	0.11
BMI	0.96	0.57, 1.35	0.8
Smoking status			
Never	—	—	
Former	1.48	0.01, 165	0.9
Current	3.18	0.09, 177	0.5
Hypertension			
No	—	—	
Yes	1.31	0.03, 50.3	0.9
Diabetus			
No	—	—	
Yes	1.82	0.05, 95.7	0.7
Preoperative creatinin	1.00	0.97, 1.02	0.8
Preoperative ureteroscopy			
No	—	—	
Yes	0.15	0.01, 1.53	0.2
Clinical stage			
cT0	—	—	
cTa/cT1	9.56	0.21, 1,215	0.3
cT2	1.00	0.01, 67.0	>0.9
cT3	0.39	0.01, 13.8	0.6
cT4	0.00		>0.9
Lymph node status CT			
No	—	—	
Lymphnodes < 1cm	6.53	0.07, 800	0.4
Hydronephrosis			
No	—	—	
Yes	2.92	0.18, 216	0.5
Surgical technique			
Open	—	—	
Laparoscopic	0.00		>0.9
Robotic	14.9	0.04, 216,564	0.5
Combination	16.7	0.15, 62,852	0.4
Side			

Left	—	—	
Right	3.09	0.22, 212	0.5
OR duration	1.01	0.99, 1.03	0.6
Lymph node dissection			
No	—	—	
Yes	0.56	0.01, 25.2	0.8
Postoperative instillation	0.36		>0.9
OR = Odds Ratio, CI = Confidence Interval			

table 5 univariable logistic regression analysis to predict the PNUT Pentafecta failure

Discussion

To our knowledge, this study is the first to propose a pentafecta tool (the PNUT) to evaluate minimally invasive or open RNU. Although, reporting surgical outcomes using dedicated tools is now commonly used in in contemporary practice, the optimal treatment of patients with high-risk UTUC remains challenging due to the rarity and practical challenges inherent to this disease. Therefore, there was an unmet need to propose a relevant tool to assess the management of this rare disease. The importance of measuring and improving surgical quality and perioperative management is well established, but it is unclear how best to accomplish these objectives. Being the pioneer to establish a tool for standardizing the outcomes in this indication, this study has the role to explore the field while improving the management and the quality of care of our patients with UTUC.

Our pentafecta includes two criteria that are related to the quality of the surgery: negative surgical margins and bladder-cuff excision. Indeed, positive surgical margins is associated with survival after RNU(1,43,44). Whatever the approach used for the RNU, some precautions should be considered during the surgery. The kidney should be removed without opening the Gerota's fascia, and opening of the urinary tract should be avoided as well as contact between instruments and the tumour(1).Therefore, following these requirements and in case of a good preoperative evaluation of the tumor, it is unlikely to get a positive surgical margin during RNU. In our study the rate of positive surgical margins was 15.6% which is in accordance with previous studies with large cohorts (44,45) especially when a "en-bloc" bladder cuff is not performed in high-risk patients. For the bladder-cuff, it is mandatory to perform a complete resection of the distal ureter and its orifice to reduce the risk of local and bladder recurrence(1,46–48). Although debates on the best specific approach for the bladder-cuff exist, the surgical approach of the ureter does not impact the risk of recurrence(19) but

the specific technique of excision might impact bladder recurrence(46). In our study, 8% of the RNU were performed without en-bloc bladder cuff. These results are encouraging regarding the standardization of the RNU technique. The bladder cuff remains one of the most important steps of this surgery and is widely recognized as quality factor of the intraoperative management(49) and was mandatory for the creation of the PNUT.

As the objective of the PNUT tool was to assess the perioperative management of high-risk patients who underwent RNU, it was important to include postoperative complications. It was decided to include hematologic and major complications based on a review of the literature. Indeed, hematologic complications were found to be the most common complication in the literature(37) and major complications is a usual key criteria for the evaluation for perioperative surgery(27,30,31,33) . In the literature, the complication rate after RNU is usually reported to be between 32-40%(28,37,50) which is in light to our study that reported 33% of complications. Similarly, the rate of major complications (15%) was similar to the usual reported rate.(37) In our study, ECOG status was higher in the PNV group. Although, ECOG was reported to be a predictor of major complications(37), ECOG was not likely to be a confounding factor in our analysis as the difference between groups was on ECOG 1 which is not considered to impact complications rate. Morevoer it was not found as a predictor of PNV in multivariate analysis. The same interpretation is also proposed for the ASA score. Although it might be debatable to implement into a perioperative assessment tool an oncological outcome, we believe that it is of utmost importance as it remains a great representation of a good management on oncology. The concept of combining oncological outcomes to was proposed by Salomon et al(51). Indeed, since few years perioperative chemotherapy and early postoperative bladder instillation are recommended(49). Although it was not possible to use these criteria in our historic cohort, because they were not used at that time, they are recognized as quality indicators for perioperative management. Therefore,

using early recurrence (<12 months) is an interesting tool to reflect these specific steps in future studies assessing RNU management. In our study the use of the PNUT has shown a great predictive value in OS and RFS when it was validated, this was an expected result that is mandatory for the use of this kind of assessment tool.

In the multivariate analysis performed to search for predictors of PNV, we did not find any preoperative patients characteristics to be involved. This a very interesting result as it suggests that the PNUT highly reflects the quality of care and the perioperative management without being impacted by patients' baseline characteristics.

Measuring and improving the quality of health care is an increasingly important goal in our contemporary practice. Patients and their families request information on outcomes, payers require health care systems to address variations in quality of care, and credentialing agencies demand evidence that hospitals – or surgeons - meet performance standards. Consequently, if its use is externally validated and accepted by our community, the use of the PNUT might be implemented as a new standard for maintenance of certification, requiring surgeons to monitor their own performance even in expert-centers. Indeed, payers in both the public and private sectors are rapidly implementing centers of excellence and pay-for-performance programs, further driving the need to systematically track and improve the quality of surgical care. Hence, stakeholders and regulation committee also track key indicators of surgical safety and monitors surgeon-specific performance as part of its credentialing process.

While the strengths of this PNUT tool remain in its innovative aspect and promising results on oncological outcomes, the study is not without limitations. First, its retrospective and multicenter design may have resulted in various in surgical technic and experience. Indeed, to be fully applicable this PNUT tool should be tested in a cohort where surgeon's experience is

known in order to relate its validation to the learning curve. In our study, the difference in surgeon expertise might have also biased the results and therefore should be assessed in other centers. Second, due to its retrospective design, all the new standards of care were not completely reflected. Perioperative systemic therapy as well as lymphadenectomy and early postoperative instillation were not performed routinely, but we believe that the use of early recurrence from all causes remains a great endpoint to reflect the perioperative oncological management for future studies. Although the number of positive lymphe nodes on final specimen was different between groups, the number of positive clinical lymphe nodes and the number of lymphe node dissection were similar. Third, we found a low rate of PV (28%), although some could debate the interest of a tool with a low validation rate, it is expected to become much higher in recent larger cohort were patients benefit from more accurate management according to recent guidelines. Finally, to fully validate this study, it is still necessary to perform an external validation in larger cohort and, if possible to implement artificial intelligence-based algorithms to validate its good predictive value in recent cohort.

Conclusion:

This study is the first to propose a tool (the PNUT) to assess perioperative management of UTUC patient at high-risk treated by RNU. Despite a low rate of validation, this pentafecta has shown a good reliability to oncological outcomes without being impacted by patients baseline characteristics suggesting its great reflection of the perioperative cares itself. Further studies are needed to externally validate the PNUT in contemporary cohorts.

Annexes

T - Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat
T4	Tumour invades adjacent organs or through the kidney into perinephric fat
N - Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes
M - Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

TNM = Tumour, Node, Metastasis (classification).

Figure 7 TNM classification for UTUC

Bibliography

1. Professionals S-O. EAU Guidelines: Upper Urinary Tract Urothelial Cell Carcinoma [Internet]. Uroweb. [cited 2020 Jun 15]. Available from: https://uroweb.org/guideline/upper-urinary-tract-urothelial-cell-carcinoma/#6
2. Almås B, Øverby S, Halvorsen OJ, Reisæter LAR, Assmus J, Carlsen B, et al. Tumour architecture, grade and location remain predictors of non-organ-confined upper tract urothelial carcinoma at time of radical nephroureterectomy: results from a multicenter Norwegian external validation study. World J Urol. 2020 Mar;38(3):717–23.
3. Soria F, Shariat SF, Lerner SP, Fritsche H-M, Rink M, Kassouf W, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). World J Urol. 2017 Mar;35(3):379–87.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018: Cancer Statistics, 2018. CA Cancer J Clin. 2018 Jan;68(1):7–30.
5. Mori K, Mostafaei H, Enikeev DV, Lysenko I, Quhal F, Kimura S, et al. Differential Effect of Sex on Outcomes after Radical Surgery for Upper Tract and Bladder Urothelial Carcinoma: A Systematic Review and Meta-Analysis. J Urol. 2020 Jul;204(1):58–62.
6. Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. Eur Urol. 2018 Jan;73(1):111–22.
7. Shariat SF, Favaretto RL, Gupta A, Fritsche H-M, Matsumoto K, Kassouf W, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol. 2011 Aug;29(4):481–6.
8. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009 Mar 15;115(6):1224–33.
9. Browne BM, Stensland KD, Moynihan MJ, Canes D. An Analysis of Staging and Treatment Trends for Upper Tract Urothelial Carcinoma in the National Cancer Database. Clin Genitourin Cancer. 2018 Aug;16(4):e743–50.
10. Jeldres C, Sun M, Isbarn H, Lughezzani G, Budäus L, Alasker A, et al. A population-based assessment of perioperative mortality after nephroureterectomy for upper-tract urothelial carcinoma. Urology. 2010 Feb;75(2):315–20.
11. Lughezzani G, Burger M, Margulis V, Matin SF, Novara G, Roupret M, et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. Eur Urol. 2012 Jul;62(1):100–14.
12. Rouprêt M, Hupertan V, Seisen T, Colin P, Xylinas E, Yates DR, et al. Prediction of cancer specific survival after radical nephroureterectomy for upper tract urothelial carcinoma: development of an optimized postoperative nomogram using decision curve analysis. J Urol. 2013 May;189(5):1662–9.
13. Benamran D, Seisen T, Naoum E, Vaessen C, Parra J, Mozer P, et al. Risk stratification for upper tract urinary carcinoma. Transl Androl Urol. 2020 Aug;9(4):1799–808.
14. Seisen T, Colin P, Rouprêt M. Risk-adapted strategy for the kidney-sparing management of upper tract tumours. Nat Rev Urol. 2015 Mar;12(3):155–66.
15. Foerster B, Abufaraj M, Matin SF, Azizi M, Gupta M, Li W-M, et al. Pretreatment Risk Stratification for Endoscopic Kidney-sparing Surgery in Upper Tract Urothelial Carcinoma: An International Collaborative Study. Eur Urol. 2021 Oct;80(4):507–15.
16. l'Urologie M de. Recommandations françaises du Comité de Cancérologie de l'AFU –

Actualisation 2018–2020 : tumeurs de la voie excrétrice supérieure [Internet]. 2019 [cited 2020 Mar 29]. Available from: https://www.urofrance.org/base-bibliographique/recommandations-francaises-du-comite-de-cancerologie-de-lafu-actualisation-15
17. Ghoneim T, Colin P, Rouprêt M. Tumeur de la voie excrétrice supérieure. 2020;12.
18. Lai S-C, Wu P-J, Liu J-Y, Seery S, Liu S-J, Long X-B, et al. Oncological impact of different distal ureter managements during radical nephroureterectomy for primary upper urinary tract urothelial carcinoma. World J Clin Cases. 2020 Nov 6;8(21):5104–15.
19. Pizzighella M, Bruyere F, Peyronnet B, Grafeille V, Brichart N, Mori K, et al. THE MANAGEMENT OF DISTAL URETER DURING RADICAL NEPHROURETERECTOMY DOES NOT INFLUENCE BLADDER RECURRENCE. J Endourol. 2021 Jun 13;
20. Roscigno M, Brausi M, Heidenreich A, Lotan Y, Margulis V, Shariat SF, et al. Lymphadenectomy at the time of nephroureterectomy for upper tract urothelial cancer. Eur Urol. 2011 Oct;60(4):776–83.
21. Roscigno M, Shariat SF, Margulis V, Karakiewicz P, Remzi M, Kikuchi E, et al. Impact of lymph node dissection on cancer specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. J Urol. 2009 Jun;181(6):2482–9.
22. Liu P, Su X, Xiong G-Y, Li X-S, Zhou L-Q. Diagnostic Ureteroscopy for Upper Tract Urothelial Carcinoma is Independently Associated with Intravesical Recurrence after Radical Nephroureterectomy. Int Braz J Urol. 2016 Dec;42(6):1129–35.
23. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet Lond Engl. 2020 Apr 18;395(10232):1268–77.
24. Fujita K, Taneishi K, Inamoto T, Ishizuya Y, Takada S, Tsujihata M, et al. Adjuvant chemotherapy improves survival of patients with high-risk upper urinary tract urothelial carcinoma: a propensity score-matched analysis. BMC Urol. 2017 Dec 1;17(1):110.
25. Freifeld Y, Ghandour R, Singla N, Woldu S, Clinton T, Kulangara R, et al. Preoperative predictive model and nomogram for disease recurrence following radical nephroureterectomy for high grade upper tract urothelial carcinoma. Urol Oncol Semin Orig Investig. 2019 Oct;37(10):758–64.
26. Krabbe L-M, Eminaga O, Shariat SF, Hutchinson RC, Lotan Y, Sagalowsky AI, et al. Postoperative Nomogram for Relapse-Free Survival in Patients with High Grade Upper Tract Urothelial Carcinoma. J Urol. 2017 Mar;197(3 Part 1):580–9.
27. the PROMETRICS 2011 Research Group, Aziz A, Gierth M, Rink M, Schmid M, Chun FK, et al. Optimizing outcome reporting after radical cystectomy for organ-confined urothelial carcinoma of the bladder using oncological trifecta and pentafecta. World J Urol. 2015 Dec;33(12):1945–50.
28. Raman JD, Lin Y-K, Shariat SF, Krabbe L-M, Margulis V, Arnouk A, et al. Preoperative nomogram to predict the likelihood of complications after radical nephroureterectomy. BJU Int. 2017 Feb;119(2):268–75.
29. Afferi L, Moschini M, Baumeister P, Zamboni S, Cornelius J, Ineichen G, et al. Trends in risk-group distribution and Pentafecta outcomes in patients treated with nerve-sparing, robot-assisted radical prostatectomy: a 10-year low-intermediate volume single-center experience. World J Urol. 2021 Feb;39(2):389–97.
30. Cacciamani GE, Winter M, Medina LG, Ashrafi AN, Miranda G, Tafuri A, et al. Radical cystectomy pentafecta: a proposal for standardisation of outcomes reporting following robot-assisted radical cystectomy: RC-pentafecta for standardised outcomes reporting after radical cystectomy. BJU Int. 2020 Jan;125(1):64–72.

31. Baron P, Khene Z, Lannes F, Pignot G, Bajeot AS, Ploussard G, et al. Multicenter external validation of the radical cystectomy pentafecta in a European cohort of patients undergoing robot-assisted radical cystectomy with intracorporeal urinary diversion for bladder cancer. World J Urol. 2021 Jul 3;
32. Afferi L, Abufaraj M, Soria F, D'Andrea D, Xylinas E, Seisen T, et al. A comparison of perioperative outcomes of laparoscopic versus open nephroureterectomy for upper tract urothelial carcinoma: a propensity score matching analysis. Minerva Urol E Nefrol Ital J Urol Nephrol. 2021 Jan 13;
33. Kahn AE, Shumate AM, Ball CT, Thiel DD. Pre-operative factors that predict trifecta and pentafecta in robotic assisted partial nephrectomy. J Robot Surg. 2020 Feb;14(1):185–90.
34. Raman JD, Jafri SM. Complications Following Radical Nephroureterectomy. Curr Urol Rep. 2016 May;17(5):36.
35. Levy A, Canes D. Perioperative complications and adverse sequelae of radical nephroureterectomy. Transl Androl Urol. 2020 Aug;9(4):1853859–1851859.
36. Geiger S, Kocher N, Illinsky D, Xylinas E, Chang P, Dewey L, et al. Comparison of the Comprehensive Complication Index and Clavien-Dindo systems in predicting perioperative outcomes following radical nephroureterectomy. Transl Androl Urol. 2020 Aug;9(4):1780–5.
37. Kocher NJ, Canes D, Bensalah K, Roupret M, Lallas C, Margulis V, et al. Incidence and preoperative predictors for major complications following radical nephroureterectomy. Transl Androl Urol. 2020 Aug;9(4):1786–93.
38. Favaretto RL, Shariat SF, Chade DC, Godoy G, Adamy A, Kaag M, et al. The Effect of Tumor Location on Prognosis in Patients Treated with Radical Nephroureterectomy at Memorial Sloan-Kettering Cancer Center. Eur Urol. 2010 Oct;58(4):574–80.
39. Lughezzani G, Jeldres C, Isbarn H, Sun M, Shariat SF, Alasker A, et al. Nephroureterectomy and segmental ureterectomy in the treatment of invasive upper tract urothelial carcinoma: a population-based study of 2299 patients. Eur J Cancer Oxf Engl 1990. 2009 Dec;45(18):3291–7.
40. Classification de Clavien [Internet]. 2016 [cited 2021 Aug 5]. Available from: https://www.urofrance.org/outils-et-recommandations/questionnaires-devaluation/classification-de-clavien.html
41. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. John Wiley & Sons; 2011. 209 p.
42. Mossanen M, Chang SL, Kimm S, Sonpavde GP, Kibel AS. Current Staging Strategies for Muscle-Invasive Bladder Cancer and Upper Tract Urothelial Cell Carcinoma. Urol Clin North Am. 2018 May;45(2):143–54.
43. Ikeda M, Matsumoto K, Hirayama T, Koguchi D, Murakami Y, Matsuda D, et al. Selected High-Risk Patients With Upper Tract Urothelial Carcinoma Treated With Radical Nephroureterectomy for Adjuvant Chemotherapy: A Multi-Institutional Retrospective Study. Clin Genitourin Cancer. 2018 Jun 1;16(3):e669–75.
44. Kenigsberg AP, Smith W, Meng X, Ghandour R, Rapoport L, Bagrodia A, et al. Robotic Nephroureterectomy vs Laparoscopic Nephroureterectomy: Increased Utilization, Rates of Lymphadenectomy, Decreased Morbidity Robotically. J Endourol. 2021 Mar;35(3):312–8.
45. Katims AB, Say R, Derweesh I, Uzzo R, Minervini A, Wu Z, et al. Risk Factors for Intravesical Recurrence after Minimally Invasive Nephroureterectomy for Upper Tract Urothelial Cancer (ROBUUST Collaboration). J Urol. 2021 Sep;206(3):568–76.
46. Xylinas E, Rink M, Cha EK, Clozel T, Lee RK, Fajkovic H, et al. Impact of distal ureter management on oncologic outcomes following radical nephroureterectomy for upper tract urothelial carcinoma. Eur Urol. 2014 Jan;65(1):210–7.

47. Xylinas E, Kluth L, Passoni N, Trinh Q-D, Rieken M, Lee RK, et al. Prediction of intravesical recurrence after radical nephroureterectomy: development of a clinical decision-making tool. Eur Urol. 2014 Mar;65(3):650–8.
48. Seisen T, Granger B, Colin P, Léon P, Utard G, Renard-Penna R, et al. A Systematic Review and Meta-analysis of Clinicopathologic Factors Linked to Intravesical Recurrence After Radical Nephroureterectomy to Treat Upper Tract Urothelial Carcinoma. Eur Urol. 2015 Jun;67(6):1122–33.
49. König F, Shariat SF, Karakiewicz PI, Mun D-H, Rink M, Pradere B. Quality indicators for the management of high-risk upper tract urothelial carcinoma requiring radical nephroureterectomy. Curr Opin Urol. 2021 Jul;31(4):291–6.
50. Lin Y-K, Deliere A, Lehman K, Harpster LE, Kaag MG, Raman JD. Critical analysis of 30 day complications following radical nephroureterectomy for upper tract urothelial carcinoma. Can J Urol. 2014 Aug;21(4):7369–73.
51. Salomon L, Saint F, Anastasiadis AG, Sebe P, Chopin D, Abbou C-C. Combined reporting of cancer control and functional results of radical prostatectomy. Eur Urol. 2003 Dec;44(6):656–60.

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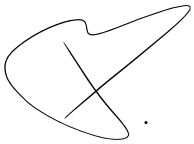

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46 pages – 5 tableaux – 7figures – 1 annexe

Résumé

Contexte : De nombreux outils ont été développés en onco-urologie avec pour but l'évaluation et l'optimisation de la prise en charge du patient. Pour la néphro-urétérectomie totale (NUT) qui est le traitement de référence des tumeurs des voies excrétrices supérieures (TVES) de haut risque (HR), aucun outil d'évaluation n'a encore été proposé. Le but de cette étude était de proposer un pentafecta afin d'évaluer la qualité de la prise en charge chirurgicale de ces patients.

Matériel et méthodes : Il s'agit d'une étude rétrospective, multicentrique dans laquelle l'ensemble des patients atteints de TVES-HR et traités par NUT dans trois centres universitaires français entre 1998 et 2020 ont été inclus dans une base de données commune. Les patients avec un suivi <12 mois, de bas risque ou présentant trop de données manquantes étaient exclus. Après analyse systématique de la littérature, un consensus entre les membres d'un groupe d'experts internationaux (YAU urothelial carcinoma working group) a été réalisé pour valider le pentafecta (PNUT). Les critères validant le pentafecta étaient : absence de complication hématologique (transfusion périopératoire, évènement thromboembolique), absence de complication majeure (Clavien Dindo ≥3) dans les 3 mois, réalisation d'une collerette vésicale, absence de marge chirurgicale et absence récidive dans l'année suivant la NUT. Nous avons défini deux groupes de patients selon la validation du pentafecta, et évalué son impact sur les résultats oncologiques.

Résultats : Parmi les 387 patients de la cohorte, 237 répondaient aux critères d'inclusion dont 67 (28%) présentaient un pentafecta validé (PV). Les caractéristiques préopératoires entre les groupes étaient similaires. Avec un suivi médian de 51 mois, la survie globale à 5 ans était supérieure chez les patients présentant un PV 80.5% (IC95% 70.7-91.7) vs 46.5% (IC95% : 38.3-56.5) pour PNV. La survie sans récidive à 5 ans était de 76.1% (IC 95% : 65.3-88.6) vs 50.4% (IC95% : 41.8-60.7) dans les groups PV et PNV respectivement ($p< 0.0001$), on observait également une meilleure survie sans métastase à 5 ans ($p<0.05$). Nous n'avons pas retrouvé dans notre population de facteurs prédictifs préopératoires d'échec du pentafecta (tous les $p> 0,05$).

Conclusion : Le pentafecta que nous avons proposé a montré que sa validation avait un impact statistiquement significatif sur les résultats oncologiques à long terme pour la survie sans récidive et la survie globale. Il pourrait être utilisé à l'avenir pour évaluer la prise en charge des patients atteints de TVES-HR. Néanmoins, une validation externe sur une plus grande population reste nécessaire pour confirmer son applicabilité.

Mots clés : Tumeurs des voies excrétrices supérieures, Haut risque, Pentafecta, néphro-urétérectomie totale

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Date de soutenance : 29/10/2021