Assessing the Impact of Old Age on Upper Tract Urothelial Carcinoma: A Retrospective Analysis from a Portuguese Tertiary Center

Avaliação do Impacto de Idade Avançada no Carcinoma Urotelial do Alto Aparelho: Uma Análise Retrospetiva de um Centro Terciário Português

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Abstract

Introduction: Upper tract urothelial carcinoma is an infrequent but aggressive disease. Radical nephroureterectomy is the standard of care for nonmetastatic tumors. The potential implications of old age in the management of upper tract urothelial carcinoma are still controversial. Our aim was to analyze the effect of old age on perioperative and oncological outcomes after radical nephroureterectomy.

Methods: We performed an observational and retrospective analysis of patients submitted to radical nephroureterectomy for nonmetastatic upper tract urothelial carcinoma in our centre between January 2018 and June 2023. Seventy-nine patients were included and divided according to their age at the time of surgery (<80 or ≥80 years old). Perioperative variables and oncological outcomes were compared between the groups. Kaplan-Meier analysis and univariable Cox regression models were used to evaluate disease-free survival, metastasis-free survival and overall survival distribution between the groups.

Results: Sixteen patients (20.5%) were aged 80 or older. We found an association between older age and a higher proportion of invasive disease (pT2 or higher; p=0.048). We also observed that omission of bladder cuff excision was more common in older patients (p=0.008). We found no differences regarding perioperative outcomes. Also, no differences in oncological outcomes, namely, disease-free survival (p=0.884), metastasis-free survival (p=0.867) and overall survival (p=0.916) were found.

Conclusion: Older age at the time of radical nephroureterectomy had no detrimental effect on perioperative and oncological outcomes. Our results suggest that older age by itself should not preclude radical nephroureterectomy.

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Resumo

Introdução: *O carcinoma urotelial do alto aparelho é uma doença agressiva, apesar de ser pouco frequente. A nefroureterectomia radical é o tratamento de eleição aquando ausência de metastização. As implicações da idade avançada no tratamento do carcinoma urotelial do alto aparelho são controversas. O objetivo deste trabalho é analisar o efeito da idade avançada nos resultados perioperatórios e oncológicos de doentes com carcinoma urotelial do alto aparelho submetidos a nefroureterectomia radical.*

Métodos: *Foi realizada uma análise observacional e retrospetiva dos doentes submetidos a nefroureterectomia radical por carcinoma urotelial do alto aparelho em fase não metastática no nosso centro, entre janeiro de 2018 e junho de 2023. Setenta e nove doentes foram incluídos e divididos consoante a idade no momento da cirurgia (<80 ou ≥80 anos de idade). As variáveis péri-operatórias e resultados oncológicos foram comparados entre os grupos. Análise de Kaplan-Meier e regressão univariável de Cox foram utilizadas para avaliar a sobrevida livre de doença, sobrevida livre de metastização e sobrevida global.*

Resultados: *Dezasseis doentes (20,5%) apresentavam 80 anos ou mais. Foi observada uma associação entre idade avançada e uma maior proporção de doença invasiva (pT2 ou mais elevado; p=0,048). Também foi observado que a omissão de cistectomia péri-meática foi mais comum nos doentes mais velhos (p=0,008). Não foram observadas diferenças nos resultados péri-operatórios. Também não foram observadas diferenças nos resultados oncológicos, nomeadamente na sobrevida livre de doença (p=0,884), sobrevida livre de metastização (p=0,867) ou sobrevida global (p=0,916).*

Conclusão: *A idade avançada no momento da nefroureterectomia radical não parece comprometer os resultados péri-operatórios ou oncológicos nos casos de carcinoma urotelial do alto aparelho. Deste modo, os nossos resultados sugerem que a ida-*

de avançada por si não deve levar à evicção de nefroureterectomia radical.

Palavras-chave: Carcinoma de Células de Transição; Idoso; Nefroureterectomia; Neoplasias da Bexiga Urinária; Neoplasias do Ureter; Recidiva Local de Neoplasia

Introduction

Upper tract urothelial carcinoma (UTUC) is an infrequent malignancy, comprising only for 5% of all urothelial carcinomas (UC).[1] It is an aggressive disease, with an estimated overall five-year cancer-specific survival (CSS) of approximately 75% after surgical treatment, with survival further decreasing in less favorable cases such as high-stage disease.[2,3] Radical nephroureterectomy (RNU) with bladder cuff excision remains the standard-of-care for non-metastatic high-risk UTUC.[4]

Life expectancy is increasing worldwide, resulting in an increase of the elderly population globally. One expected consequence of this global ageing is an increase in cancer diagnosis.[5] This may be of particular relevance for UTUC given its estimated peak incidence between 70 and 90 years old.[1,6]

The risk-benefit balance between surgical aggression and potential gains in oncological control is particularly challenging in the elderly. This directly translates to the management of UTUC. RNU is a major surgery with considerable perioperative risks, but it is also the only curative option for an aggressive disease. Previous studies regarding the management of UTUC in the elderly population and, more precisely, the applicability of RNU in this particular population, have shown inconsistent findings. Firstly, worse oncological outcomes, such as inferior CSS and overall survival (OS), were observed by some authors in the older patients.[7-9] These results support the notion that older age imposes a negative influence in the outcome of UTUC. However, other works have not found this detrimental effect of old age.[10-12] More specifically, these studies presented similar results regarding recurrence-free survival (RFS) and CSS between younger and older patients.

In our work, we aim to analyze a population of nonmetastatic UTUC patients submitted to RNU and elucidate the role of advanced age in the perioperative and oncological outcomes. Our main hypothesis is that older age does not confer, by itself, worse oncological outcomes. We also hypothesize that older age may confer worse perioperative outcomes.

Methods

Population

An observational and retrospective study was performed by reviewing the clinical records of all patients diagnosed with non-metastatic UTUC and submitted to RNU with curative intent in our centre between January 2018 and June 2023. Seventy-nine cases were identified and divided according to age at surgery: i) less than 80 years old (group 1, n=63); ii) 80 or more years old (group 2, n=16). This age cutoff was chosen mainly for two reasons. First and foremost, it aligns with the Portuguese life expectancy[14]. Additionally, we consider the 80 years threshold more challenging regarding surgical decision than other cut-offs seen in the literature, such as the 70-year mark. Surgical approach (open or laparoscopic) was discussed at the department's meeting in a case-by-case basis before the intervention. The bladder cuff excision (BCE) technique was not standardized and decided by the senior surgeon. Template-based lymph node dissection (LND) was performed when bulky nodal disease was identified at staging computerized tomography or intraoperatively. Two patients underwent adjuvant chemotherapy, while neoadjuvant chemotherapy was not used.

Demographics, clinical and tumor-specific variables including gender, previous history of UC, presence of ureterohydronephrosis (UHN), tumor location (renal pelvis, ureter or both), size of lesion (categorized as smaller or larger than 2 cm), multifocality and previous radical cystectomy status were collected and analyzed. Surgical details, such as the surgical approach (open or laparoscopic) and the method of BCE were also studied. Pathological characteristics were also assessed, with tumor staging according to TNM classification of AJCC[15] and tumor grading by WHO.[16] Other pathological variables assessed were the presence of histological subtypes,[16] lymphovascular invasion (LVI), carcinoma *in situ* (CIS) and margin status.

We evaluated perioperative outcomes between groups, namely: any complications, classified by Clavien-Dindo (CD) classification,17 major complications (CD≥3), reintervention rate, perioperative mortality and transfusion rate. Operative time and hospital stay duration were also compared. Patients submitted to synchronous radical cystectomy were excluded from the perioperative analysis.

Oncological outcomes were also analyzed. Follow-up of the patients was performed as standardized in our institution, with cystoscopy, urine cytology and computed tomography (with urography) performed routinely in a risk-based schedule. The events studied were local recurrence, bladder recurrence, metastization and death. We also performed a survival analysis regarding disease-free survival (DFS), defined as the time between nephroureterectomy and the occurrence of any of the previous events except for bladder recurrence, metastasis-free survival (MFS), defined as the time between nephroureterectomy and the finding of metastasis, and overall survival (OS), defined as the time between nephroureterectomy and death from any cause.

We defined as our primary endpoints for the oncological outcomes analysis DFS and MFS distributions according to age at

the time of surgery. Also, for the perioperative analysis, rate of overall complications was defined as the primary outcome.

Statistical Analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation or median; IQR (interquartile range) as appropriate. Chi-square ($\chi 2$) or Fisher's exact tests were used for categorical variables. T student test and Mann-Whitney U test were performed for continuous variables, whether with or without normal distribution, respectively. The distribution of disease-free survival, metastasis-free survival and overall survival was estimated using the Kaplan–Meier analysis with log-rank test. A univariable Cox regression model was also performed for disease-free survival, metastasis-free survival and overall survival. A *p*-value inferior to 0.05 was considered statistically significant. Analyses were performed with the IBM SPSS Statistics v.26 for Windows software (IBM Corp, Armonk, NY).

Results

Table 1 shows the demographics, clinical and surgical data of the 79 patients with nonmetastatic upper tract urothelial carcinoma

Table 1 – Demographic, clinical and surgical characteristics and their association with age at the time of surgery for the 79 patients submitted to radical nephroureterectomy for upper tract urothelial carcinoma

	<80 years (n=63)	≥80 years (n=16)	*p*-value[a]
Median age (y); IQR	69; 13	84; 5	-
Median follow-up (mo); IQR	21; 29	22; 21	0.834
Male, *n (%)*	49 (77.8)	8 (50)	0.057
Previous UC, *n (%)*	15 (23,8)	1 (6,3)	0.170
UHN, *n (%)*	30 (47.6)	7 (43.8)	1
Lesion >2 cm, *n (%)*	48 (76.2)	11 (68.8)	0.535
Tumor location			0.050
Renal pelvis, *n (%)*	42 (66.7)	9 (56.3)	
Ureter, *n (%)*	20 (31.7)	4 (25)	
Both, *n (%)*	1 (1.6)	3 (18.8)	
Laterality			0.586
Left, *n (%)*	29 (46)	6 (37.5)	
Right, *n (%)*(93.8)		34 (54)	10 (62.5)
Multifocality, *n (%)*	13 (20.6)	3 (18.8)	1
Previous Cy, *n (%)*	4 (6.3)	-	0.354
Surgical approach			0.056
Open, *n (%)*	19 (31.1)	1 (6.3)	
Laparoscopic, *n (%)*	42 (68.9)	15	
Bladder cuff management			0.008
Open cuff excision, *n (%)*	29 (52.7)	6 (40)	
Laparoscopic cuff excision, *n (%)*	11 (20)	-	
Laparoscopic ureterectomy without cuff excision, *n (%)*	4 (7.3)	6 (40)	
Endoscopic excision, *n (%)*	11 (20)	3 (20)	

Y - years; **mo** - months; **IQR** – interquartile range; **UC** – urothelial carcinoma; **UHN** – ureterohydronephrosis; **Cy** – cystectomy.

[a] Mann-Whitney U test for continuous variables. Fisher's exact test and Chi-square test (presence of UHN and laterality) for categorical variables.

submitted to radical nephroureterectomy. Sixteen (20.5%) patients were older than 80 years at the time of RNU, with a median age of 84 years (Interquartile range of 5 years). Follow-up was available for 78 patients (one patient from group 2 lost follow-up) with an average time of 26 ±2.1 months. We observed a trend favoring female sex in the older patients (22.8% *vs* 50%; *p*=0.057), and also between older age and evidence of disease in both renal pelvis and ureter (*p*=0.050). All the other clinical characteristics at presentation were similar between the groups, namely history of UC or radical cystectomy before the diagnosis of UTUC, UHN at the time of diagnosis, a lesion size greater than 2 cm or disease multifocality. Regarding surgical management, although not statistically significant, a minimally invasive approach (transperitoneal laparoscopic) was preferred in the elderly patients (93.8% (15/16) *vs* 68.9% (42/63); *p*=0.056). Bladder cuff management at the time of the RNU was significantly different between the groups (*p*=0.008), with a higher proportion of patients in the elderly group submitted to RNU without formal bladder cuff excision (7.3% *vs* 40%).

The pathological features of the RNU specimens are summarized in Table 2. A higher tumor stage was observed in the older patients, with 81.3% (13/16) being pT2 or higher, against 52.4% (33/63) in group 1 (*p*=0.048). Other pathological features were not statistically different between the groups.

The perioperative results are shown in Table 3, while Table 4 depicts the oncological results. There were no differences between the groups regarding any outcome studied. Furthermore, there were no differences regarding disease-free survival, metastasis-free survival and overall survival between the two groups studied (Fig. 1).

Oncological Results of Omission of Bladder Cuff Excision

Regarding the subgroup of elderly patients managed without bladder cuff excision, these showed an average age of 85.8±1.2 years. The majority were female (83.3% (5/6)), with an isolated tumor of the renal pelvis (66.7% (4/6)). 83.3% (5/6) of the cases were pT2 or higher. Follow-up was only available for 5 patients, for

Table 2 – Pathological features and their association with age at the time of surgery for the 79 patients submitted to radical nephroureterectomy for upper tract urothelial carcinoma

	<80 years (n=63)	≥80 years (n=16)	*p*-value[a]
pT stage			0.452
T0, *n (%)*	3 (4,8)	–	
Ta, *n (%)*	11 (17.5)	1 (6.3)	
T1, *n (%)*	16 (25.4)	2 (12.5)	
T2, *n (%)*	10 (15.9)	3 (18.8)	
T3, *n (%)*	18 (28.6)	7 (43.8)	
T4, *n (%)*	5 (7.9)	3 (18.8)	
pT≥2, *n (%)*	33 (52.4)	13 (81.3)	0.048
LA (pT3-4 and/or pN+), *n (%)*	24 (38.1)	10 (62.5)	0.095
Positive surgical margin, *n (%)*	7 (11.1)	4 (25)	0.219
Tumor grade			0.234
Dysplasia, *n (%)*	2 (3.2)	–	
Low grade, *n (%)*	–	1 (6.3)	
High grade, *n (%)*	61 (96.8)	15 (93.8)	
Histological subtype, *n (%)*	16 (25.4)	5 (31.3)	0.753
Lymphovascular invasion, *n (%)*	17 (27)	7 (43.8)	0.229
CIS, *n (%)*	16 (26.2)	3 (18.8)	0.747

LA – locally advanced; **CIS** – carcinoma in situ

[a] Fisher's exact test and Chi-square test (distribution of pT≥2 disease or LA disease) for categorical variables.

Table 3 – Perioperative results and their association with age at the time of surgery for the 70 patients submitted to radical nephroureterectomy for upper tract urothelial carcinoma without synchronous radical cystectomy

	<80 years (n=55)	≥80 years (n=15)	*p*-value[a]
Complication (CD)			0.541
No, *n (%)*	40 (72.7)	9 (60)	
I, *n (%))*	3 (5.5)	1 (6.7)	
II, *n (%)*	9 (16.4)	4 (26.7)	
III, *n (%)*	1 (1.8)	1 (6.7)	
IV, *n (%)*	-	-	
V, *n (%)*	2 (3.6)	-	
Major complication (CD≥3), *n (%)*	3 (5.5)	1 (6.7)	1
Reintervention, *n (%)*	3 (5.5)	1 (6.7)	1
Perioperative mortality, *n (%)*	2 (3.6)	-	1
Transfusion, *n (%)*	4 (7.3)	2 (13.3)	0.602
Mean operative time ± SD (min)	173.8 ± 7.1	181 ± 15.7	0.651
Median hospital stay (d); IQR	6; 3	6; 2	0.816

CD – Clavien-Dindo; **SD** – standard deviation; **min** – minutes; **d** – Days; **IQR** – interquartil range.
[a] Mann-Whitney U and T student tests for continuous variables. Fisher's exact test for categorical variables.

Table 4 – Oncological outcomes and their association with age at the time of surgery for the 78 patients submitted to radical nephroureterectomy for upper tract urothelial carcinoma with adequate follow-up

	<80 years (n=63)	≥80 years (n=15)	*p*-value[a]
Local recurrence, *n (%)*	9 (15)	2 (13.3)	1
Bladder recurrence, *n (%)*	10 (18.2)	3 (20)	1
Distant recurrence, *n (%)*	17 (28.3)	4 (26.7)	1
Death, *n (%)*	20 (32.3)	5 (33.3)	1

[a] Fisher's exact test for categorical variables.

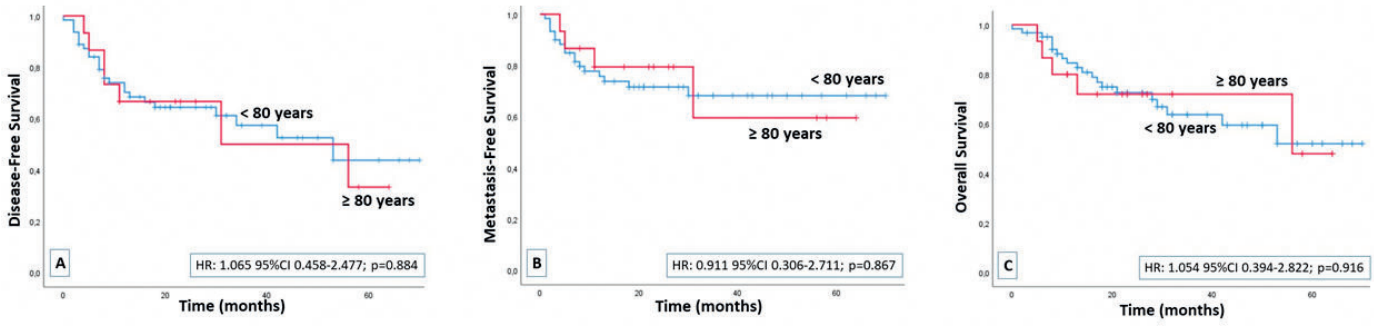

Figure 1 – Kaplan–Meier plots of survival analyses according to age at surgery (<80 *vs* ≥80 years old) for: disease-free survival (A); metastasis-free survival (B) and overall survival (C)

an average time of 16.6 ± 5.4 months. Bladder recurrence, local recurrence, metastization and death (of any cause) occurred in 2/5 patients (40%), with only one patient out of five remaining totally disease-free during the entire follow-up.

Given the omission of bladder cuff excision in these patients, the surgical margin status is a matter of particular interest. Three cases (out of 6) had positive surgical margins. However, one case had locally advanced disease (pT4) with positive surgical margin only at the perirenal fat, with disease progression and death in five months. Other case also had a locally advanced disease (pT4) with positive surgical margin both in perirenal fat tissue and ureter margin. This patient has lost follow-up. The third patient had a microscopic positive margin of the ureteric stump. This patient developed local recurrence at 8 months, and was managed with ureterectomy of the remnant ureter. Bladder recurrence followed at 15 months, which was managed with transurethral resection, being currently without evidence of disease.

Discussion

The impact of old age in the management of UTUC remains a controversial topic in our work, we retrospectively analyzed a population of elderly UTUC patients regarding perioperative and oncological outcomes. We found no significant differences between the two age groups in our primary endpoints for oncological outcomes, namely, DFS (p=0.884) and MFS (p=0.867), supporting our hypothesis that advanced age, by itself, may not confer worse oncological outcomes for UTUC. Also, the other oncological outcomes, such as OS distribution, local recurrence, bladder recurrence, distant recurrence and death of any cause, were similar between the groups, further supporting our hypothesis. We hypothesized, however, that older age would confer worse perioperative results, namely with a higher overall surgical complications rate. This was not the case, with a non-statistical difference between the groups, not only in our primary endpoint of overall complications, but also in all other perioperative outcomes. These results would let us conclude that age by itself does not pose a detrimental effect on perioperative results. However, this conclusion must be made with caution, given the fact that the two subgroups are not truly comparable regarding the surgical approach and bladder cuff excision method, which limits this analysis.

The implications of advanced age in the management and outcomes of UTUC have already been studied by several authors, although with contradictory results. Shariat *et al,*[7] in a multicentric study with 1453 patients, found an association between older age and worse CSS and OS. The same results were observed in a study by Chromecki *et al,*[8] in a study with more than 1000 patients, with older age being associated with worse RFS, CSS and OS. More recently, in a large multicentric Italian study, Ferro *et al*[9] found the same results, with older age associated with worse CSS and OS. It is noteworthy, however, that differences in patient management were observed between older and younger patients. Firstly, in all the studies, adjuvant chemotherapy was less frequently used in elderly patients. Also, elderly patients were less frequently submitted to LND in the two older studies.[7,8] These discrepancies in patient management led the authors to raise the possibility that suboptimal management in the elderly patients may have also contributed to the worse outcomes found. In line with that hypothesis, in the study of Chromecki *el al*,[8] after adjusting for the ECOG performance status, the impact of age in RFS and CSS was no longer observed. This led the authors to conclude that chronological age per se is not a contraindication for RNU. Furthermore, Teoh *et al*[18] showed in their work that being submitted to RNU was associated with better DFS regardless of age. Although this gain was more pronounced in younger patients, it was also observed in the older ones. Therefore, the authors concluded that RNU should always be considered when deemed feasible. Additionally, considering that older patients are less likely to undergo chemotherapy, the authors highlight the potential curative effect of RNU in this subset of patients.

Other works found an absence of clinical impact of age in the outcomes of UTUC. Ye *et al*[10] studied 588 UTUC patients to whom a RNU was performed and observed no differences in CSS between older and younger patients. Similar results regarding CSS were found by Yamada *et al*,[11] Koterazawa *et al*,[12] and Ishikawa *et al*.[13] These works also reported on RFS, that was similar between the two age groups. Inferior OS was reported in two studies,[11,12] with an inferior survival being attributed by the authors to other-cause mortalities. Perioperative complications and outcomes were only analysed in the work of Koterazawa *et al*.[12] These were similar between older and younger patients, underlining the feasibility of RNU in the elderly population.

Our work is not without limitations, that must be acknowledged. First of all, the retrospective design of the study is a limitation given the inherent shortcomings of this design. There is also a potential selection bias based on surgical eligibility, mainly in the elderly group. It is possible that the present cohort of elderly patients may not represent the entire population aged above 80 years old. Another limitation is the fact that a comprehensive analysis of comorbidities and functional status was not taken into account. Also, it can be pointed as a limitation the relatively small number of patients in our series. Despite this being true, it represents the experience of a high-volume centre, ensuring a more standardized follow-up and perioperative management, a limitation commonly seen in other works. Another limitation is the chosen age cut-off of 80 years old. This fact represents a limitation since that, in the literature, different age thresholds are chosen by different authors. This lack of uniformity limits the direct compa-

rison and external applicability of all these studies and ours as well.

Another limitation is the unstandardized performance of LND and also the unstandardized management of the bladder cuff during RNU. Bladder cuff excision is a matter of extreme controversy. The uncertainties reside not only in the superiority between surgical techniques, but also in the real benefit of performing the cuff excision. Bladder cuff management has, in the one hand, been shown to be an important factor influencing intravesical recurrence.[19-21] On the other hand, the same authors found that RFS, CSS and OS outcomes were not influenced by bladder cuff management.[19] The same results were found recently in the work of Yong *et al*[22] where the omission of BCE did not influence MFS, CSS or OS but was associated with an increase in bladder recurrence. Therefore, although the unclear effect on survival, BCE is considered part of the standard-of-care procedure for UTUC, given the increased risk of bladder recurrence derived from its omission. However, it is not universally performed. This is observed in large multicentric retrospective studies, where the percentage is less than 75%.[23,24]

These uncertainties regarding the oncological benefit of BCE are even more significant in patients with an isolated urothelial tumor of the renal pelvis. Lughezzani *et al*[23] analysed more than 4000 patients with a renal pelvic tumour and found an association between the omission of the excision of bladder cuff and worse cancer specific mortality, but only in locally advanced disease. However, as it is pointed out by Zlotta[25] this finding is quite perplexing given the fact that these patients are expected to progress to distant recurrence irrespective of the bladder cuff excision. It is also noteworthy that the patients in which the bladder cuff excision was not performed were older, with higher pT stage, higher tumor grade and also with significantly higher proportion of nodal involvement, which may interfere with the findings. Conversely, other authors found that the omission of the bladder cuff excision may not compromise oncological outcomes. Nazzani *et al*[24] performed a large multicentric retrospective study based on the SEER database. The authors analysed more than 4000 patients with T1-T3 renal pelvic urothelial tumors and found that the omission of bladder cuff excision did not influence CSS or other cause mortality.

In our series, we observed a higher proportion of elderly patients in whom bladder cuff excision was omitted. These patients were extremely old and with a very high proportion of muscle-invasive disease. Although with a very small number and therefore without power for statistical analysis, some considerations can still be made. Firstly, the option of sparing the bladder cuff resulted in evident suboptimal surgery in two cases, given the positive margin in the ureteric stump. One of these patients had a worse outcome directly due to that decision, with local and bladder recurrence with need of a deferred ureterectomy and transurethral resection. However, this patient was thereafter without evidence of disease. Secondly, we must also observe that the rate of any oncological event, more importantly, distant progression, was 40%, which was slightly higher than in the overall series, even in the presence of a shorter follow-up time. The very low number of patients and the very aggressive histology found in these patients, higher than the overall series, precludes drawing conclusions regarding the possible impact of BCE on progression and in our series. On another note, the impact of BCE omission in the perioperative outcomes was not studied. If a more favourable perioperative profile were to be seen with the omission of BCE, one could argue that it may justify the inferior local and bladder control, assuming that survival will not be affected. Although this represents an enticing hypothesis, our work is unable to provide answers in this regard, with further studies with a larger number of patients being needed.

Conclusion

In conclusion, the perioperative and oncological outcomes showed no difference between older and younger patients with UTUC. Our results suggest that age in itself should not preclude RNU for nonmetastatic UTUC if the patient is deemed fit-for-surgery. Additionally, a less aggressive surgery, by omitting the excision of bladder cuff in selected tumors of the renal pelvis, may be a surgical option with a more favorable risk-benefit ratio for older patients, albeit still needing further studies for its validation.

Responsabilidades Éticas

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FPG, FL (F. Lopes), RF, IB: Conceção, interpretação dos dados para o trabalho; elaboração do trabalho, revisão e aprovação final da versão a ser publicada.

JC (J. Correia), JC (J. Carvalho), JSM, VS, FL (F. Lobo), AM: Revisão e aprovação final da versão a ser publicada.

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