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ORIGINAL PAPER

# Is robotic radical nephroureterectomy a safe alternative to open approach: The first prospective analysis

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**Summary** ***Purpose: To test the efficacy and safety profile of robotic radical nephroureterectomy compared to the open approach.***
***Methods: We enrolled 45 consecutive patients who suffered from non-metastatic, upper urinary tract urothelial carcinoma from September 2019 to March 2021 and underwent radical nephroureterectomy. Patients were divided in two groups: group A consisted of 29 patients (open approach) and group B consisted of 16 patients (robotic approach). The factors which were taken into consideration were age, sex, body mass index, tumour size, side and grade, cancer stage, ASA score, operation time, drain removal time, foley time, hospitalization time, estimated blood loss, surgical margins, preoperative and postoperative creatinine, Hct and bladder recurrences. Statistical analysis was performed with the use of SPSS version 26 and $p < 0.05$ was the cut-off for reaching statistical significance.***
***Results: The mean age in group 1 was 67.12 years and in group 2 68.12 years, whereas the mean body mass index (BMI) in group 1 was 26.54 kg/m$^2$ and in group 2 25.20 kg/m$^2$. Operative time was better in group A (124 vs 186 mins $p < 0.001$) and estimated blood loss were better in group B compared to group A (137 vs 316 ml $p < 0.001$). Length of stay (LOS) was significantly less in the robotic group (5.75 vs 4.3 days $p = 0.003$) and the same applied for time required for drain removal (4.5 vs 3.3 days $p = 0.006$).***
***Conclusions: Robotic radical nephroureterectomy is a safe and efficient alternative to open approach. It provides a favorable perioperative profile in patients suffering from upper urinary tract carcinoma without metastasis.***

KEY WORDS: *Robotic radical nephroureterectomy; Open radical nephroureterectomy; Prospective analysis; Complications.*

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## INTRODUCTION

*Upper urinary tract urothelial carcinoma* (UUTC) represents a relatively rare entity, as it accounts for 5% of these neoplasms with an estimated annual incidence of 2 cases per 100.000 inhabitants (1), but because 60% of these malignancies are invasive at the time of diagnosis their management is of crucial importance (2). According to *European Association of Urology*, *open radical nephroureterectomy* (ORNU) with bladder cuff excision remains the gold standard treatment of high-risk UTUC, regardless of tumour location (3). Trying to improve safety and effectiveness of treatment, new techniques such as laparoscopy have become an effective alternative (4-6). The results have shown that both laparoscopic nephroureterectomy and hand-assisted laparoscopic nephroureterectomy had comparable, if not superior, perioperative and postoperative and similar oncological outcomes (6).
Technological advances made to achieve shorter and less morbid operations, have led to the next step of UTUC treatment, which is the use of the robotic platform. Results from multiple studies and the experience of various surgeons worldwide has shown that RRNU share equivalent oncologic outcomes at short-term follow up, while also displaying very low peri-operative morbidity and complications (7, 8). Although *robotic radical nephroureterectomy* (RRNU) represents a promising alternative to currently existing methods of treatment, there is a surprising paucity of studies comparing RRNU and ORNU. All available data originate from retrospective studies limited by important selection biases. Our study represents the first prospective comparison of these two techniques regarding their efficacy and safety in the treatment of UTUC.

## MATERIALS AND METHODS

We enrolled 45 consecutive patients who suffered from non-metastatic, upper urinary tract urothelial carcinoma from September 2019 to March 2021 and underwent radical nephroureterectomy. The surgeries took place in two different academic centres by experienced surgeons. In the former, the operations were performed by three different surgeons, each of whom had performed more than 50 open nephroureterectomies. In the latter, all the operations were carried out by the same surgeon with a vast experience in robotic upper tract surgeries (more than 300). Patients were divided in two groups: group A consisted of 29 patients (open approach) and group B consisted of 16 patients (robotic approach).
The exclusion criteria of the patients for the study were the following: patients with history of other urological managements and patients with contraindications for laparoscopic surgery. The *Institutional Review Board* has approved the study protocol and all patients have signed an informed consent.

No conflict of interest declared.

The Da Vinci Xi System was used for the robotic procedures. We followed the same technique for performing RRNU as already published (9). Open NU procedures were based on the standard approach 2 with bladder cuff excision (10). The factors which were taken into consideration were age, sex, body mass index, tumour size, side and grade, cancer stage, ASA score, operation time, drain removal time, Foley time, hospitalization time, estimated blood loss, surgical margins, preoperative and postoperative creatinine, Hct and bladder recurrences. Complications were categorized according to Clavien Dindo system (11).
Continuous variables are described as mean ± *standard deviation* (SD) and categorical variables as proportions. Comparison of continuous outcomes was performed using Student's t-test for normally distributed data and Mann-Whitney test for non-normally distributed data. Distribution of data was checked using the Shapiro-Wilk test. Categorical variables were compared between the two groups, using chi-square and Fisher's exact test, as dictated by the frequency of observations. Statistical analysis was performed with the use of SPSS version 26 and $p \leq 0.05$ was the cut-off for reaching statistical significance.

## Results

The study included 45 patients from which 7 were female (5 in group A and 2 in group 2) and 38 males. The basic characteristics of the patients are shown in Table 1.
The mean age in group 1 was 67.12 years and in group 2 68.12 years, whereas the mean *body mass index* (BMI) in group 1 was 26.54 kg/m$^2$ and in group 2 25.20 kg/m$^2$, without any statistically significant difference between them. A right sided tumor was found in 13 patients in group A and 4 patients in group B, whereas 14 patients in group A and 10 in group B had tumors in the renal calyces or pelvis. The two groups were matched in terms of ASA score ($p = 0.07$) and tumor size ($p = 0.5$).
Operative time was better in group A (124 *vs* 186 mins $p < 0.001$) and estimated blood loss were better in group B compared to group A (137 *vs* 316 ml $p < 0.001$). Two patients in group A and no patient in group B required transfusion. *Length of stay* (LOS) was significantly less in the robotic group (5.75 *vs* 4.3 days $p = 0.003$) and the same applied for time required for drain removal (4.5 *vs* 3.3 days $p = 0.006$). The peri- and postoperative results are shown in Table 2. In group A, 16 patients suffered postoperative complications: 7 patients suffered from fever, 2 from hematoma, 3 from wound infection, 2 required transfusion, 1 from paralytic ileus and 1 suffered a myocardial infarction whereas from group B 3 patients suffered postoperative complications, 2 patients with fever and 1 with hematoma. The complications' classification according to Clavien-Dindo score is shown in Table 3.

***Table 1.***
*Basic patients characteristics.*

| | Group A (n = 29) | Group B (n = 16) | P value |
|---|---|---|---|
| Age (years) | 67.12 (12.19) | 68.12 (9.0) | 0.8 |
| Sex (male/female) | 24/5 | 14/2 | 1.0 |
| BMI (kg/m$^2$) | 26.54 (1.95) | 25.20 (1.85) | 0.12 |
| Tumor size (mm) | 36.2 (20.09) | 33.0 (10.73) | 0.59 |
| Laterality (right) | 13 | 4 | 0.71 |
| Tumor location intra renal | 14 | 10 | 0.06 |
| Ureter | 15 | 6 | |
| ASA score | 2.56 (0.89) | 2.06 (0.25) | 0.07 |
| Preoperative creatinine (mg/dl) | 1.16 (0.43) | 1.23 (0.30) | 0.09 |
| Preoperative Hct | 38.85 (4.91) | 41.71 (3.52) | 0.06 |

*ASA score (American Society of Anesthesiologists score); BMI (body mass index).*
*Continuous outcomes are presented as mean values (± standard deviation).*

***Table 2.***
*Peri and postoperative outcomes.*

| | Group A | Group B | P value |
|---|---|---|---|
| Operative time (min) | 124,37 (25.74) | 186.25 (34.03) | < 0.001 |
| Drain removal time (days) | 4.5 (1.21) | 3.3 (0,94) | 0.006 |
| Foley removal time (days) | 11.43 (5.29) | 3,37 (0.80) | < 0.001 |
| Length of stay (days) | 5.75 (1.43) | 4.3 (1.08) | 0.003 |
| Estimate blood loss (ml) | 316.87 (93.87) | 137.5 (78.52) | < 0.001 |
| Positive surgical margins | 8/29 | 0/16 | 0.004 |
| Postoperative creatinine (mg/dl) | 1.4 (0.47) | 1.43 (0.39) | 0.8 |
| Postoperative Hct | 31.90 (4.37) | 37.71 (4.05) | 0.003 |
| Pathological T stage | | | 0.01 |
| Ta | 5 | 6 | |
| T1 | 9 | 2 | |
| T2 | 1 | 3 | |
| T3 | 13 | 5 | |
| T4 | 1 | 0 | |
| Tumour grade | | | 0.06 |
| Low grade | 8 | 9 | |
| High grade | 21 | 7 | |
| Bladder recurrence | 3 | 1 | 0.33 |

***Table 3.***
*Post-operative complications.*

| Clavien Dindo classification | Group A | Group B | P value |
|---|---|---|---|
| No complications | 13 | 13 | 0.28 |
| Grade I | 12 | 1 | |
| Grade II | 3 | 2 | |
| Grade III | 0 | 0 | |
| Grade IV | 1 | 0 | |
| Grade V | 0 | 0 | |

## Discussion

The use of the robotic platform for the management of UUTC has evolved since the first reports of retroperitoneal (12) and intraabdominal operations (13, 14) that may have also utilized other approaches (open or laparoscopic) for the nephrectomy or the ureterectomy. The surgeon's experience has increased and new "*hybrid*" techniques have emerged, eliminating the basic disadvantage of the robotic platform, namely the need for redocking to perform ureteral excision (15, 16). Robotic approach yielded satisfactory oncological outcomes, even for

advanced disease, with studies reporting a 5-year recurrence free survival of 57.1% in a series including 28.3% patients with pT3 and 6.7% pT4 disease (17). In the same pace, one of the biggest studies so far enrolling patients from three high volume robotic surgery centers, reported a low high grade complication rate (2.6%) with excellent intra- and post-operative results, suggesting this approach as a viable alternative to the gold standard open approach (18). The technology advancements of the robotic platform with the development of the DaVinci Xi system provided the surgeon's more tools towards increasing experience in this approach, while decreasing operation room time (19).

Recently published data in the literature, emphasize the auxiliary role of robotic radical nephroureterectomy in the management of UUTC. The next step was comparing this approach to the open technique, which remains the gold standard therapy according to global guidelines. Available data in existing literature, consist of studies that enrolled patients mainly from open and pure laparoscopic approaches, while robotic approach cases in these series represented a minority. Even though some of these studies have large sample sizes, all of them are retrospective and their level of evidence is relatively low, due to the inherited bias of the retrospective nature (20, 21).

In another study, multivariate logistic regression revealed a significant favorable impact of robotic approach in postoperative complications but not for intraoperative ones (22). As for the functional outcomes of the procedure, it is documented in the literature that RNU may be a risk factor for acute kidney injury resulting in renal function decline after this procedure (23). In our cohort, in both groups, patients suffered from postoperative creatinine decline, nevertheless when the two groups were compared no statistically significant difference was found relative to this factor. A relatively recent study provided data for the oncological superiority of the robotic approach, since this approach showed significantly longer progression free, cancer specific and overall survival ($p < 0.05$) (6). Nevertheless, in this study the open surgeries were performed in patients of most advanced stage and with negative prognostic factors (like lymph node metastasis).

A recent systematic review and meta-analysis of a vast number of patients provided useful insights on the comparison of the open, laparoscopic, and robotic approach: the RRNU showed the lowest *estimated blood loss* (EBL) and the ONU the highest (163 ml *vs* 419.99 ml) with ONU showing higher odds of transfusion. Operative time was shorter for ONU whereas RRNU showed both lower *length of stay* (LOS) and intraoperative complications. Nevertheless, the meta-analysis is significantly limited from the retrospective studies which were analyzed (only 1 RCT and 2 prospective studies none of which included robotic cases) and most patients included were derived from non-comparative studies.

Consequently, in this meta-analysis the distribution is in favor of ONU and LRNU so the data on robotic technique might be weak (24).

Our study represents the first prospective comparison between open and robotic approach. The two groups were matched for most significant factors that could affect final outcomes, except from T stage, which it is not likely to have an impact to most of perioperative outcomes. We found a favorable profile of the robotic approach when compared to its open counterpart: better LOS, EBL, Hct decrease, need for transfusions and removal of drains and catheters. We also found significant difference in positive surgical margins, but this is possible due to the most advanced stage of tumors that were operated with the open approach. The basic difference from the literature is operation time which was lesser in the open approach but again this can be justified because the robotic approach requests docking of the robot and changing of the instruments position for the ureterectomy.

The small sample size comprises a limitation of this study, necessitating the conduct of larger prospective cohorts, ideally after patient randomization. Nevertheless, this limitation is partly equilibrated by the prospective nature of our study and the limitation of potential biases that it provides. Another potential limitation is the relatively short follow-up (1-5 months), but the study was designed to address the efficacy and safety of these procedures by comparing their perioperative outcomes.

## Conclusions

Robotic radical nephroureterectomy is a safe and efficient alternative to open approach. It provides a favorable perioperative profile in patients suffering from upper urinary tract carcinoma without metastasis. Future prospective or randomized trials can assess its efficiency versus open approach in terms of oncological outcomes.

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