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Simple enucleation for the treatment of highly complex renal tumors: Perioperative, functional and oncological results

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Abstract

Aim: To assess the role of simple enucleation (SE) for the treatment of highly complex renal tumors.
Methods: Overall, 96 Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification score 10 to 13 renal tumors were treated with SE at our institution. All conventional perioperative variables, surgical, functional and oncological results were gathered in a prospectively maintained database. Survival curves were generated using a Kaplan–Meier method. Univariate analysis assessed the outcome differences.
Results: Mean (±1s.d.) clinical tumor diameter was 4.8 (±1.6 cm). 70.8% of patients had ≥cT1b stage. The PADUA score was recorded as 10, 11, 12 and 13 in 57.3%, 29.2%, 11.5%, and 2.1% of tumors respectively. Overall, 76 patients were treated with an open approach and 20 robotically. Mean warm ischemia time (WIT) was 19.2 min, and WIT greater than 25 min occurred in 14.6% of cases. Positive surgical margin (PSM) rate was 3.6% and trifecta was achieved in 64.3% of patients. Postoperative surgical complications occurred in 24% of patients, with 14.6% Clavien-Dindo grade 1–2, 8.3% grade 3, and 1% grade 4. Five-year cancer specific survival (CSS), recurrent free survival (RFS), and overall survival (OS) rates resulted 96.1%, 90.8% and 88.0%, respectively. Overall, 4.2% of patients experienced progressive disease. At follow-up, the mean decrease of eGFR from preoperative value was 13.9 ml/min. This was not significantly correlated with PADUA score ($p = 0.69$). The surgical approach was neither a predictor of Trifecta outcome, nor of postoperative complications, WIT >25 min or PSM rate.
Conclusions: SE is an effective treatment for highly-complex renal tumors, with a potential key role to widen the NSS (nephron sparing surgery) indications according to guidelines.

Keywords: Renal cancer; Nephron sparing; Simple enucleation; Nephrometry; Partial nephrectomy

Introduction

Surgery remains the mainstay of renal cell carcinoma (RCC) management. Nephron-sparing surgery (NSS) reduces the risk of chronic kidney disease (CKD) development and may decrease the incidence of postoperative cardiovascular and metabolic sequelae. Onocological outcomes appear equivalent to radical nephrectomy (RN).[1] However the adoption of such surgery has been low; especially for large and highly complex cT1 tumors.[2,3] From a surgical perspective, the complexity of kidney tumors, insufficiently discriminated by tumor size alone,[4] is measured by nephrometric scores. The 'Preoperative Aspects and Dimensions Used for an Anatomical' (PADUA) classification is one of the most widely used.[5] To treat challenging cases (PADUA≥10 and cT1b), some authors have reported lower surgical complexity when using simple enucleation (SE).[6–8] SE, either performed as open and robotic approach,[9] involves the excision of an RCC without any visible rim of healthy parenchyma around it. This is achieved by a blunt

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dissection of the natural cleavage plane between tumor capsule and healthy parenchyma. The efficacy of SE is supported by studies showing good functional preservation, a low rate of postoperative CKD, and similar long-term oncological results to those of standard PN.[10–12] Nevertheless, no previous studies have evaluated the results of this technique in highly complex tumors. The aim of the present study is to assess perioperative, functional and oncological results of SE in a series of tumors with PADUA score ≥10.

Patients and methods

Patient selection

Consecutive patients treated with SE in our department between July 2006 and August 2013 for clinically localized RCC were gathered in a prospectively maintained database. Those with PADUA ≥10 tumors and were selected for this study. Both those treated with standard open simple enucleation (OSE) and 20 with Endoscopic Robotic-Assisted Simple Enucleation (ERASE) were included.[9] The approach selection was based not on the surgical complexity but on chronological criteria, as ERASE was preferred since January 2011, with the exception of patients with previous extensive transperitoneal surgery.

Surgical technique

For these challenging cases the following technical assessments were used: (1) an accurate study of tumor and renal vasculature through three-dimensional reconstruction CT scan (preoperative imaging was readily available for review also during surgery), (2) intraoperative ultrasound guidance to delineate or confirm the tumor limits of mainly endophytic tumors.

Open simple enucleation

OSE was approached by a lombotomic incision, as previously reported.[8] Briefly, the renal pedicle was usually controlled en bloc with vascular clamps. Renal hypothermia was not induced. The natural cleavage plane between the pseudocapsule and normal parenchyma was developed by blunt dissection using a peanut, after having incised the renal capsule few millimeters away from the surface tumor limits. Any tears in UCS or vessels in the enucleation bed were repaired with running sutures. The parenchymal defect was closed with horizontal interrupted sutures, after application of haemostatic agents.

Robotic simple enucleation

A transperitoneal approach was used for ERASE, with the patient in a flank position. A miniopen access was used for a 12 mm periumbilical trocar placement and pneumoperitoneum was created. A conventional configuration with two robotic arms was used, as previously shown.[9] Two or three additional trocars for the bed-assistant were used: one 10–12 mm trocar, one 5 mm trocar and, in case of right kidney, a subxifoid 5 mm port to retract the liver. After docking the S/Si DaVinci robot (Intuitive Surgical, Sunnyvale,USA), the bowel was retracted medially, Gerota's fascia was incised and the kidney completely mobilized. The hilum was identified and renal artery and vein were isolated. The tumor template was marked with monopolar cautery. The intracorporeal US guidance (standard laparoscopic US controlled by the bedside assistant or a drop-in robotic US probe controlled by the console) was used to confirm mainly/completely endophytic tumor burdens. Ischemia was obtained in most of the cases by bulldog clamp of the main artery. The lesion was blunt enucleated using Maryland bipolar forceps on the left hand to push the tumor upward. The monopolar scissors (closed), controlled by the right hand, alternated the blunt dissection of the enucleation plane (done with a gentle pressure on the capsulated tumor tissue with the back of the instrument) and the coagulation of small parenchymal vessels (done with the tip). Hemostasis in the resection bed was achieved with running sutures (Monocryl 2/3-0), according to the sliding clip technique.[13] Care was taken to repair all visible opened calices and bleeding sites, before placing hemostatic agents and closing the cortical defect with sutures.

Data collection

All conventional perioperative (pre-, intra- and postoperative) variables were collected, including nephrometry, warm ischemic time (WIT), estimated blood loss (EBL), operative time, length of stay (LOS), medical and surgical complications (occurring within 30 days of discharge) stratified via a Clavien-Dindo system.[14] Blood loss with need for transfusion, superselective embolization, or re-intervention was registered. Urinary fistula was recorded in cases of persistent drainage leakage beyond the seventh postoperative day with a fluid biochemical analysis consistent with urine (drainage fluid-to-serum creatinine ratio greater than 2). The change in laboratory parameters between pre-operative, discharge, and follow-up were measured, including the estimated glomerular filtration rate (eGFR) (calculated with Modification of Diet in Renal Disease equation[15]). Surgical specimens were processed in accordance with standard procedures by two expert uropathologists. Pathological tumor size, 2009 TNM stage,[16] Fuhrman nuclear grade,[17] positive surgical margin (PSM) and histological subtypes according to World Health Organization classification[18] were registered. The Trifecta rate was calculated as the combination of WIT <25 min, negative surgical margins, and no complications.[19]

Follow-up

The patients' status was last evaluated in February 2014. The follow-up schedule comprised biochemical profiling

(including eGFR), chest X-ray and either ultrasound or CT scan of the abdomen, performed alternately, every 6 months after surgery for the first 3 years and yearly thereafter. Bone scintigraphy was performed only in case of clinical suspicion. Patients were assessed periodically after surgery during an office visit or by telephone to evaluate their status and the imaging requested.

Statistical analysis

Continuous parametric variables are presented as mean ± standard deviation (SD), nonparametric as median and interquartile range (IQR), and categorical with frequencies and proportions. The probability of survival was estimated by Kaplan–Meier method. Recurrence-free survival (RFS) was determined from the day of surgery to the time of recurrence (local or distant) confirmed by an imaging technique. Cancer-specific survival (CSS) and overall survival (OS) were determined from the day of surgery to the death from cancer, or from all cause, respectively, or to last follow-up. Univariate analysis (Pearson's chi square, unpaired or paired t test, Mann–Whitney U test) assessed the differences of perioperative variables between ERASE and OSE, and evaluated the association of surgical, functional, and oncological results with PADUA score, stratified according to the median value as 10 vs. ≥11. An additional univariate analysis appraised the correlation of WIT ≥25 min and eGFR reduction, in the entire series and in the subgroup with relative/imperative indications, analyzed separately. All tests were two-tailed, with a statistical significance at $p < 0.05$. All data were analyzed with the Statistical Package for Social Sciences software, v.17.0 (SPSS Inc., Chicago,IL,USA).

Results

510 consecutive patients were treated with SE in our department between July 2006 and August 2013. Of these, 96 had PADUA ≥10 tumors and were selected for this study. 76 treated with standard open simple enucleation (OSE) and 20 with Endoscopic Robotic-Assisted Simple Enucleation (ERASE).[9]

Preoperative, surgical and pathologic data of 96 patients are reported in Table 1. Mean ± SD clinical tumor diameter was 4.8 ± 1.6 cm, and 70.8% of patients had T1b clinical stage, or higher. Overall, 63.5% were <50% exophytic and 25.0% completely endophytic. The PADUA score was 10, 11, 12 and 13 in 57.3%, 29.2%, 11.5%, and 2.1% of tumors respectively. Preoperatively, 19.8% of patients had chronic kidney disease stage 3 or above, and 20.8% were operated with an imperative/relative indication. Mean WIT and operative time were 19.2 and 126 min, respectively, with a median LOS of 6 days. The percentage of patients with postoperative complications was 24.0%. 2.1% were Clavien-Dindo stage 1, 12.5% stage 2, 8.3% stage 3, 1% stage 4). Clavien-dindo stage 3 complications required 5

Table 1
Perioperative variables of patients with highly complex renal tumors treated with SE.

Preoperative variables	Total
N	96
Age, yrs mean ± SD	64 ± 13
Male gender no. (%)	59 (61.4%)
BMI median (IQR)	24.8 (23.1–27.2)
Charlson index median (IQR)	1 (0–2)
Relative/imperative indication no. (%)	20 (20.8%)
Patients with preop. CKD stage ≥3 no. (%)	19 (19.8%)
Preoperative eGFR (ml/min) median (IQR)	79 (64–97)
Clinical diameter (cm) mean ± SD (range)	4.8 ± 1.6 (3–10)
PADUA score no. (%)	
10	55 (57.3%)
11	28 (29.2%)
12	11 (11.5%)
13	2 (2.1%)
Tumor size score/Clinical stage no. (%)	
≤4 cm	28 (29.2%)
4.1–7 cm	59 (61.5%)
>7 cm	9 (9.3%)
Middle longitudinal location no. (%)	49 (51.0%)
Medial rimno. (%)	40 (41.7%)
≥50% exophytic tumor no. (%)	11 (11.5%)
<50% exophytic tumor	61 (63.5%)
Completely endophytic tumor	24 (25.0%)
Involved urinary collecting system no. (%)	85 (88.5%)
Involved renal sinusno. (%)	80 (83.3%)
Intraoperative outcomes	
Clamping of renal pedicle/artery no. (%)	95/96 (99.0%)
WIT (min) mean ± DS (range)	19.2 ± 5.7 (9–38)
WIT > 25 minno. (%)	14 (14.6%)
EBL (cc)mean ± DS	196 ± 125
Operative time (min) mean ± DS	126 ± 46
Total intraoperative complications no. (%)	3 (3.1%)
➢Transfusions	1 (1.0%)
➢Spleen lesion (repaired with haemostatic agents)	1 (1.0%)
➢Ureteral lesion (sutured)	1 (1.0%)
Postoperative outcomes	
LOS (days, including the day of surgery) median (IQR)	6 (5–7)
Postoperative overall complicationsno. (%)	25/96 (26.1%)
Postoperative medical complicationsno. (%)	2/96 (2.1%)
Postoperative surgical complicationsno. (%)	23/96 (24.0%)
➢Postop. transfusions (Clavien 2)	12 (12.5%)
➢Selective embolization (Clavien 3a)	5 (5.2%)
➢Reoperation for bleeding (Clavien 3b)	1 (1.0%)
➢Urinary fistula without stenting (Cl.1)	2 (2.1%)
➢Urinary fistula with stenting (Cl.3a)	2 (2.1%)
➢Splenectomy for spleen lesion (Cl. 4)	1 (1.0%)
➢Clavien 5	–
Major (Clavien 3–4) complicationsno. (%)	9 (9.4%)
Delta Hb (3rd postop − Baseline) (g/dL) mean ± DS	2.7 ± 1.3
3rd postop eGFR (g/dL) median (IQR)	68 (51–82)
Pathologic assessment	
Benign tumors no. (%)	12/96 (12.5%)
Pathological T stage no. (%)	
pT1a	43/84 (51.2%)
pT1b	24/84 (28.6%)
pT3a	17/84 (20.2%)

Table 1 (*continued*)

Preoperative variables	Total
Fuhrman nuclear grade no. (%)	
Grade 1–2	65/84 (77.4%)
Grade 3–4	19/84 (22.6%)
Positive surgical margins no. (%)	3/84 (3.6%)
Patients with trifecta no. (%)	54/84 (64.3%)

superselective arterial embolization, 1 reoperation for bleeding, and 2 ureteral stenting for urinary fistula. We performed a splenectomy for postoperative bleeding following a splenic injury (Clavien 4 complication). Benign tumors accounted for 12.5% of patients. Positive surgical margin (PSM) rate was 3.6% (3/84). The Trifecta outcome was achieved in 64.3% of patients. At the univariate analysis no significant difference resulted in ERASE vs. OSE group regarding all preoperative variables (including the distribution of nephrometric subscores), with the exception of BMI which was significantly higher in ERASE group ($p = 0.02$). The surgical approach was not a predictor of postoperative complications, WIT >25 min, PSM rate, and trifecta outcome.

Functional results are expressed in Table 2 and Fig. 1. Preoperatively, median (IQR) eGFR was 79 (64–97) ml/min; eGFR decreased to 68 (51–82)ml/min on the third postoperative day, and partially recovered to 76 (56–88) ml/min one month after surgery. At the last point of follow up mean eGFR was 66 (50–81) ml/min, with a mean decrease from preoperative value of 13.9 ± 25.0 ml/min after a mean follow-up of 54 months. Compared to preoperative value, the eGFR reduction at each postoperative visit was significantly decreased ($p < 0.0001$). At the last follow-up visit 29/85 (34%) patients had stage 3–5 CKD, up 14.2% from baseline. In the entire series, WIT≥25 min did not significantly correlate with eGFR reduction ($p = 0.64$), while it significantly correlated with eGFR reduction in the subgroup with relative/imperative indications ($p = 0.009$).

Table 2
Oncological and functional data at latest follow-up.

Follow-up (months) mean ± SD (range)	54 ± 26 (15–91)
Patients with available follow-up no. (%)	85/96
Oncological data	
Patients with recurrence no. (%)	4/85 (4.7%)
Local recurrence no. (%)	1 (1.2%)
Distant recurrence no. (%)	3 (3.5%)
5yy Recurrence-free survival(%)	90.8%
5yy Cancer-specific survival(%)	96.1%
5yy Overall survival (%)	88.0%
Functional data	
Preoperative eGFR (ml/min) median (IQR)	79 (64–97)
Stage 1–2 CKD (eGFR >60) no. (%)	77/96 (80.2%)
Stage 3–4 CKD (eGFR 15–59) no. (%)	19/96 (19.8%)
Stage 5 CKD (eGFR <15) no. (%)	0
Latest eGFR (ml/min) median (IQR)	66 (50–81)
Stage 1–2 CKD (eGFR >60) no. (%)	56/85 (65.9%)
Stage 3–4 CKD (eGFR 15–59) no. (%)	28/85 (33.0%)
Stage 5 CKD (eGFR <15) no. (%)	1 (1%)
Difference in eGFR (preop. − latest) mean (DS)	13.9 ± 25.0
Patients with acquired stage 3–5 CKD at follow-up, compared to preoperative (%)	+14.2%

Oncological results are summarized in Table 2 and Fig. 2. Mean follow-up was 54 (14–96) months. Overall, 11 patients were lost to follow-up and excluded from the analysis. During this period 7 patients died, two of whom died of RCC, and 5 of causes independent of RCC. The mean time to tumor-unrelated death was 41 (21–74) months. The mean time to cancer-specific death was 30 (17–42) months. The 5-year CSS, RFS, and OS rates resulted 96.1%, 90.8% and 88.0%, respectively. Overall, 4 (4.2%) patients experienced progressive disease. One patient (1.2%), with a PSM, had local recurrence 50 months after SE, underwent salvage nephrectomy and was free from disease at the last follow-up. Three patients experienced distant metastases (3.5%) with no evidence of local recurrence. Of these, two died 17 and 42 months after surgery, and the third one is alive under therapy with tyrosine kinase inhibitors.

On univariate analysis, PADUA score 10 versus ≥11 resulted significantly associated with the achievement of trifecta and with negative surgical margin, but not with WIT, complications rate, recurrence rate nor with the decrease of eGFR from baseline (Table 3).

Discussion

Standard PN is still underused in RCC with adverse nephrometry, with a frequent recourse to RN also in high-volume centers. A recent analysis on 1400 patients stratified the treatment choice (PN vs.RN) of 19 surgeons from 3 American centers by tumor complexity, and showed great variability for intermediate and high complexity tumors. PN was chosen in 75–100% of low nephrometry tumors, in 0–100% of intermediate-, and in 0–45% of high-complexity tumors.[2] This variability indicates that many surgeons are concerned in the short-term by complex reconstructions, worse surgical outcomes and higher rate of complications related to high-risk RCC.[20] Some authors suggested a possible advantage of using SE, particularly when facing tumors with the most unfavourable nephrometry profiles. In this respect SE may reduce the surgical switch from PN to RN.[6–8] Our perioperative results show that SE has the potentiality to widen the NSS indication to challenging cases. Indeed, we confirm good surgical results of SE in highly complex RCC, with a mean WIT of 19.2 min, mean EBL of 200cc, and trifecta achievement in 64.3% of patients. Postoperative surgical complications occurred in 24% of patients, but 14.6% were Clavien grade 1–2 as bleeding treated with bedrest and transfusions, while only 9.4% were major surgical complications. In a previous study on 65 robotic PN for completely endophytic RCC, mean WIT, EBL, complications rate and trifecta achievement resulted 21.7 min, 226cc, 9.2%, and 60%,

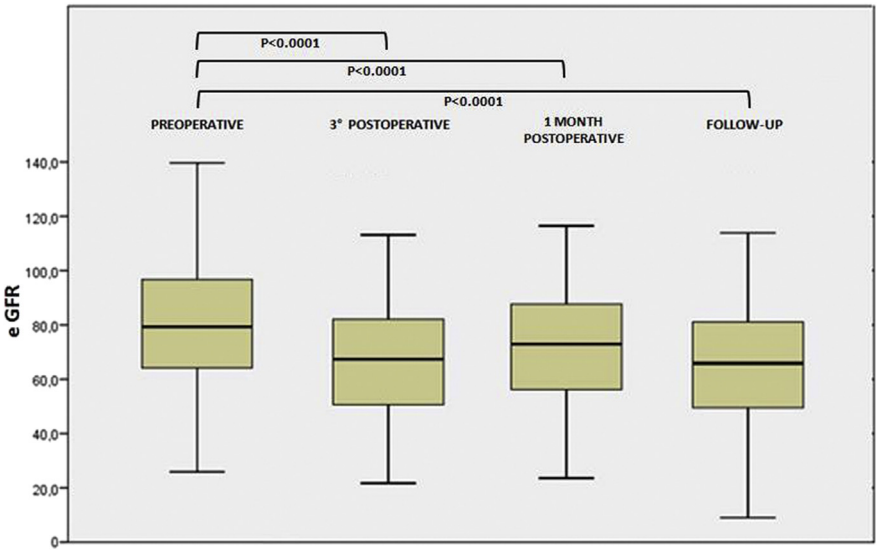

Figure 1. Boxplot chart showing estimated glomerular filtration rate (eGFR) modifications according to different evaluations: preoperative, third postoperative day, one month postoperative, and latest follow-up (54 ± 26 months).

respectively,[21] with a morbidity apparently much lower. However, in this study only the 35.4% had high-risk nephrometry, and the mean tumor diameter was 2.5 cm.

Other concerns about NSS in highly complex renal tumors may relate to long-term results, as functional recovery. Some authors found that an high nephrometry score is an independent risk factor for de novo CKD stage 3 or above after standard PN[22] and that tumors classified as highly complex (R.E.N.A.L.≥10) were associated with minor functional volume preservation, and lower percent eGFR preservation.[23] In the present study we show an eGFR reduction of only 13.9 ml/min from baseline after a mean of 54 months. We did not found nephrometry score to significantly predict eGFR decline. These data, taken together, indicate that SE may give the maximum preservation of healthy parenchyma possible in highly complex cases. For the purpose of preservation, SE seems to be less dependent on nephrometry compared to standard PN. Our results are strengthened by studies that reaffirmed the importance of the thickness of healthy parenchyma excised along with tumor for the long-term renal function preservation after NSS.[24] Simmons et al. showed that percent kidney volume preservation and not WIT was the primary determinant of ultimate eGFR after PN, and found that technical modifications aimed at minimizing healthy volume loss, while still achieving negative margins, may result in improved functional outcomes.

A worse oncological outcome has been postulated in highly complex renal tumors, and in this regard SE might have a further negative effect. After PN, an high tumor complexity was associated with higher grade malignancy,[25] and with pathological tumor up-staging.[26] Few studies on highly complex RCC are available, and most with short follow-up, therefore whether the correlation between adverse pathological findings/poor survival outcome and higher nephrometry score is stronger than that with higher TNM stage is still debated. In a study on 80 patients treated

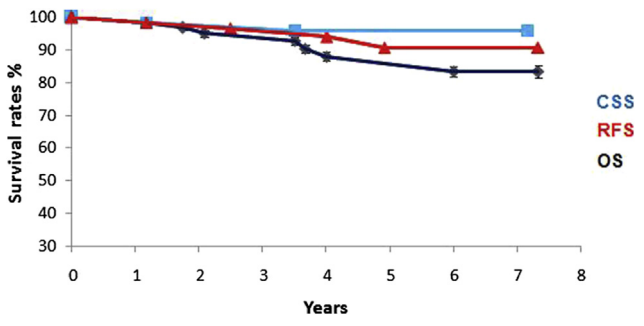

Figure 2. Recurrence-free survival (RFS), cancer-specific survival (CSS) and overall survival (OS) estimated with the Kaplan–Meier method.

Table 3
Correlation analysis between PADUA and surgical, functional and oncological results.

Result	PADUA 10	PADUA 11-13	P
N (%)	55 (57.3%)	41 (42.7%)	–
Warm ischemia time (WIT)mean ± SD	18.6 ± 5.7	20.5 ± 5.9	0.12
Postoperative complication rate no. (%)	13/55 (23.6%)	12/41 (29.3%)	0.88
Clavien-dindo (stage 3–4) complication rate no. (%)	4/55 (7.3%)	5/41 (12.2%)	0.21
Positive surgical margin (PSM) no. (%)	1/48 (2.1%)	2/36 (5.5%)	0.047
Patients with trifecta no. (%)	36/48 (75%)	18/36 (50%)	0.035
Tumor recurrence rate no. (%)	2/55 (3.6%)	2/41 (4.9%)	0.85
eGFR (ml/min) reduction: preop. - last follow-up mean ± SD	12 ± 20.3	14.3 ± 30.4	0.69

with PN for cT2 RCC at a median follow-up 41.5 months, high-risk nephrometry was negatively associated with OS, and provided additional risk assessment beyond clinical T stage.[27] In another study of 19 RPN in RCC with moderate-high nephrometry score,[28] no increased progression rate was found, but with a median follow-up of 22 months only. In the current study, 5 year RFS and CSS were 90.8% and 96.1% respectively. The corresponding survivals in a series of SE with no selection for tumor diameter and complexity were 94.8% and 98.2%, respectively.[29] In a series selected for stage (T1b), 5 year CSS after SE was 83.3%.[8] These data suggest that SE is oncologically safe in high-risk tumors, and that the adverse nephrometry may have a limited pejorative role on the oncological outcomes, with a lower relevance than tumor stage. Further studies with larger series and longer follow-up with a specific aim to compare the prognostic role of the nephrometric scores with the consolidated prognostic role of the TNM system are needed to investigate whether a high nephrometry independently affects oncological results of NSS.

SE can be effectively performed both as OSE and ERASE.[9] In the current analysis the surgical approach resulted associated neither with Trifecta nor with its constituents. This suggests that perioperative results of ERASE are not inferior to OSE also in this clinical settings. However, comparison between OSE and ERASE was not one of the aims of the present study and this must be considered as a preliminary result. Larger series with longer follow-up of the robotic arm are needed for a reliable comparison of oncological and functional results.

The limits of this study include its retrospective analysis, although data were carefully collected in a prospectively maintained database. We also did not include the R.E.N.A.L. or the C-Index in the evaluation of adverse nephrometry. However, to date the PADUA score is the only nephrometric tool that has been validated for the SE.[30]

In conclusion, SE is an effective treatment for highly-complex renal tumors. It has a low rate of major complications, is oncologically safe, allows a good preservation of renal function. This may contribute to a widening of the indications for NSS according in future guidelines.

Conflict of interest statement

All authors have nothing to disclose.

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None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2015.02.019.

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