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Simple enucleation versus standard partial nephrectomy for clinical T1 renal masses: Perioperative outcomes based on a matched-pair comparison of 396 patients (RECORd project)

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Abstract

Objectives: To compare simple enucleation (SE) and standard partial nephrectomy (SPN) in terms of surgical results in a multicenter dataset (RECORd Project).

Materials and methods: patients treated with nephron sparing surgery (NSS) for clinical T1 renal tumors between January 2009 and January 2011 were evaluated. Overall, 198 patients who underwent SE were retrospectively matched to 198 patients who underwent SPN. The SPN and SE groups were compared regarding intraoperative, early post-operative and pathologic outcome variables. Multivariable analysis was applied to analyze predictors of positive surgical margin (PSM) status.

Results: SE was associated with similar WIT (18 vs 17.8 min), lower intraoperative blood loss (177 vs 221 cc, $p = 0.02$) and shorter operative time (121 vs 147 min; $p < 0.0001$). Surgical approach (laparoscopic vs. open), tumor size and type of indication (elective/relative vs absolute) were associated with WIT >20 min. The incidence of PSM was significantly lower in patients treated with SE (1.4% vs 6.9%; $p = 0.02$). At multivariable analysis, PSM was related to the surgical technique, with a 4.7-fold increased risk of PSM for SPN compared to SE. The incidence of overall, medical and surgical complications was similar between SE and SPN.

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Conclusions: Type of NSS technique (SE vs SPN) adopted has a negligible impact on WIT and postoperative morbidity but SE seems protective against PSM occurrence.

Introduction

In the last decades, a net increase in the detection of small incidental renal masses has been observed and nephron-sparing surgery (NSS), aimed to preserve the largest amount of healthy renal tissue while obtaining similar oncologic outcomes of radical nephrectomy (RN), has become more popular.[1,2] Standard partial nephrectomy (SPN) consisting in the tumor removal with an adequate safety margin of health parenchyma is still considered as the gold standard technique.[3] In the last decades, some Authors demonstrated that healthy parenchyma surrounding the tumor can be limited to a few millimeters without compromising the oncologic safety of partial nephrectomy (PN).[4] Although the mean thickness of the safety margin surrounding the tumor ranges from 2.5 mm to 5 mm, some studies clearly demonstrated that the minimum values of thickness of the safety margin ranges between 0 mm and 1 mm above all at the bottom of the tumor.[1] This variability of the thickness of the safety margin might be influenced by several anatomical and topographic tumor features. In this context, some Authors proposed the simple enucleation (SE) of the tumor as alternative to the SPN.[5] This surgical procedure consists of a blunt dissection of the renal tumor following a plane between the capsule and the healthy renal tissue, without including any visible normal renal parenchyma. Recently, a multicenter, retrospective analysis reported similar cancer specific and recurrence free survival rates after SE and SPN.[5] However, in the previous study no data concerning perioperative outcomes were reported. The objective of present study was to compare intraoperative and early post-operative outcomes observed in two recent cohort of patients who underwent SE or SPN for parenchymal renal masses.

Materials and methods

The Italian Registry of Conservative Renal Surgery (RECORd Project) is an observational multicenter prospectively derived dataset promoted by the Leading Urological No profit foundation Advanced research (LUNA) of the Italian Society of Urology. Patients who underwent open or laparoscopic PN for clinical T1 renal tumors between January 2009 and January 2011 at 19 urological Centers were collected in the registry and included into the study. The study was approved by the Internal Board Committee and all patients signed a specific informed consent. Exclusion criteria were: incomplete data and presence of synchronous metastatic disease. All the clinical records were collected in an online database consisting of 5 main sections (demographic, preoperative, intraoperative, postoperative and histopathological findings). Performance status was defined according to the Eastern Cooperative Oncology Group (ECOG) criteria.[6] Mode of presentation of the tumor was defined according to the Patard classification.[7] Moreover, tumors were classified according to their location on the longitudinal plane (polar or mesorenal). Each tumor was also classified into three growth pattern categories: 1) prevalently (=50%) exophytic, 2) prevalently endorenal (<50% exophytic), and 3) entirely endorenal. Indications to NSS were defined as elective (localized unilateral renal mass with healthy contralateral kidney), relative (localized unilateral renal mass with concomitant co-morbidities such as diabetes, hypertension or lithiasis) and absolute (bilateral tumors, multiple tumors, moderate to severe chronic kidney disease or tumors involving solitary kidneys). NSS was performed as SPN or SE according to surgeon's and center's preferences independently form tumor characteristics and surgical complexity. SPN consisted in the complete tumor excision with of an additional visible margin of healthy renal parenchyma. SE was defined as a blunt tumor excision performed without a visible rim of parenchyma tissue around tumor pseudocapsule.[5] Haemostasis of the excision bed was achieved with different haemostatic agents (Floseal®, Tachosil®, Cianacril®, Tabotamp® and fibrin glue®). The following intraoperative data were recorded: type of surgical approach (open or laparoscopic), NSS technique (SPN or SE), operative time, presence or absence of ischemia, ischemia time, intraoperative blood loss, and intra-and early post-operative complications. All surgical specimens were processed by experienced uro-pathologists at each institution. All the tissue blocks were embedded in paraffin, sectioned, and stained with hematoxylineosin. Microscopic evaluation allowed the assignment of histological type and nuclear grade, pathological stage, and evaluation of surgical margins. Tumors were clinically and pathologically staged according to the American Joint Committee on Cancer (AJCC) TNM classification.[8] Heidelberg and Fuhrman classifications were used to assign the tumor histologic subtype and the nuclear grade, respectively.[9,10] For surgical margins evaluation the specimens (both SE and SPN specimens) were fixed in 10% buffered formalin, and grossly analyzed. The size, the colour, the gross aspect (solid to cystic) were recorded, and the surgical margin was marked with ink. After tumor dissection, samplings were

performed in order to obtain tissue blocks where tumor, renal parenchyma, and surgical edges were comprised and further blocks where tumor, renal capsule, and peritumoral fat were enclosed. The margin was considered positive when tumor tissue was marked with ink. The margin was considered negative when no-neoplastic renal tissue was observed between tumor tissue and the line of ink. All postoperative medical and surgical complications occurring within 30 days from surgery were recorded. The severity of surgical complications was graded according to the modified Clavien classification system.[11] In the present study a propensity score matching was performed to adjust for preoperative variables using R Project. This is a method that permits to control for imbalances in confounding factors among discrete study cohorts.[12,13] A propensity score was calculated for each patient using multivariable logistic regression based upon the covariates: clinical tumor size (continue variable), type of indication, surgical approach, tumor growth pattern and tumor location. The matching was carried out with a 1:1 ratio with respect to the treatment (SPN vs SE) with a C statistic of 0.9. Continuous variables were reported as mean, standard deviation (SD), median and range as appropriate. Categorical variables were reported as percentages. The Student t test was used to compare continuous variables. The Pearson chi square test was used to compare categorical variables. The SPN and the SE group were compared regarding pre-operative, intra-operative, pathologic and early post-operative outcome variables. Multivariable logistic regression models were applied to assess predictors of positive surgical margin (PSM) status. Statistical significance was set as $p = 0.05$. All reported p values are two sided. Analyses were performed with SPSS version 17.0 (SPSS Inc, Chicago, IL, USA) by two of the authors (AM, AM).

Results

Overall, 198 patients that underwent SPN were matched with 198 patients that underwent SE. Demographics and tumors' characteristics are reported in Table 1. The two study groups were comparable in terms of: mean age, body mass index, gender, ECOG performance status, clinical tumor size, symptoms at diagnosis, type of indication, growth pattern, tumor location, glomerular filtration rate, hemoglobin level. The only difference that emerged between the two groups was the side of the tumor. Most patients in both groups underwent open surgery, with only 36.9% of SE and 32.8% of SPN performed laparoscopically (Table 1). Operative time was significantly lower in the SE group (121 min vs 147 min; $p < 0.0001$). Hilar clamping was done in 122 patients (61.7%) in the SPN group and in 138 patients (69.7%) in the SE group. Mean ischemia time was 18 min and 17.8 min in the SE and SPN groups, respectively (p: not significant). WIT was = 20 min in 103 patients (74.6%) in the SE group and in 92 patients (75.4%)

Table 1
Preoperative and intra-operative data.

	Standard partial nephrectomy	Simple enucleation	p
Age			
Mean, SD	62.4 (12.2)	62.8 (11.5)	n.s.
≤65 n, (%)	95 (48.0%)	99 (50.0%)	n.s.
>65 n, (%)	103 (52.0%)	99 (50.0%)	
BMI, Mean (SD)	26.4 (3.9)	26.5 (3.9)	n.s.
Gender			
Male n, (%)	141 (71.2%)	124 (62,6%)	n.s.
Female n, (%)	57 (28.8%)	74 (37.4%)	
Tumor side			
Right n, (%)	118 (59.6%)	87 (43.9%)	0.007
Left n, (%)	79 (39.9%)	109 (55%)	
Bilateral n, (%)	1 (0.5%)	2 (1.1%)	
ECOG			
0 n, (%)	122 (61.6%)	116 (58.6%)	n.s
≥1 n, (%)	76 (38.4%)	82 (41.4%)	
Symptoms at diagnosis			
Asymptomatic n, (%)	161 (81.3%)	172 (86.9%)	n.s.
Symptomatic n, (%)	37 (18.7%)	26 (13.1%)	
Clinical tumor size, mean (SD)	3.0 (1.4)	3.0 (1.2)	n.s.
Clinical tumor size			
≤4 cm n, (%)	168 (84.8%)	166 (83.8%)	n.s.
4.1–7 cm n, (%)	30 (15.2%)	32 (16.2%)	
Tumor location			
Polar n, (%)	140 (70.7%)	137 (69.2%)	n.s.
Mesorenal n, (%)	58 (29.3%)	61 (30.8%)	
Type of indication			
Elective n, (%)	166 (83.8%)	172 (86.9%)	n.s.
Relative n, (%)	16 (8.1%)	10 (5.0%)	
Absolute n, (%)	16 (8.1%)	16 (8.1%)	
Tumor growth pattern			
≥50% exophytic n, (%)	152 (76.8%)	149 (75.2%)	n.s.
>50% endophytic n, (%)	44 (22.2%)	47 (23.8%)	
Completely endorenal n, (%)	2 (1.0%)	2 (1.0%)	
Preop GFR using MDRD, mean (SD)	82.3 (21.9)	85.6 (23.0)	n.s.
Preoperative HB level, mean (SD)	14.1 (1.5)	14.2 (1.4)	n.s.
Surgical approach			
Open n, (%)	133 (67.2%)	125 (63.1%)	n.s.
Laparoscopic n, (%)	65 (32.8%)	73 (36.9%)	
Hilar clamping			
Yes n, (%)	122 (61.7%)	138 (69.7%)	n.s.
No n, (%)	76 (38.3)	60 (30.3%)	
Ischemic time (min) mean (SD)	17.8 (6.9)	18 (5.5)	n.s.
Operative time (min) mean (SD)	147 (42)	121 (44)	$p < 0.0001$
Intraoperative blood loss (cc), mean (SD)	221 (131)	177 (128)	$p = 0.02$

SD: Standard deviation.
BMI: Body mass index.
ECOG: Eastern Cooperative Oncology Group.
Hb: Hemoglobin.
GFR: Glomerular filtration rate.
MDRD: Modification of diet in renal disease.

Table 2
Univariate analysis for WIT >20 min in 260 patients that had NSS with hilar clamping.

	WIT ≤20 min	WIT >20 min	P
Age, mean (SD)	62.3 (12.1)	61.6 (12.8)	0.68
Tumor size (cm), mean (SD)	3.1 (1.3)	3.7 (1.4)	0.0004
Surgical approach, n. (%)			<0.0001
VLP	48 (53.3%)	42 (46.7%)	
Open	147 (86.5%)	23 (13.5%)	
Surgical technique, n. (%)			0.89
SE	103 (74.6%)	35 (25.4%)	
PN	92 (75.4%)	30 (24.6%)	
Tumor growth pattern, n. (%)			0.94
≥50% exophytic	137 (74.9%)	46 (25.1%)	
>50% endophytic	58 (75.3%)	19 (24.7%)	
Tumor location, n. (%)			0.43
Polar	110 (76.9%)	33 (23.1%)	
Mesorenal	85 (72.6%)	32 (27.4%)	
Symptoms at diagnosis, n. (%)			0.93
Asymptomatic	161 (74.9%)	54 (25.1%)	
Symptomatic	34 (75.6%)	11 (24.4%)	
Indication, n. (%)			0.07
Elective	171 (76.7%)	52 (23.3%)	
Relative	12 (80%)	3 (20%)	
Absolute	12 (54.5%)	10 (45.5%)	
Indication, n. (%)			0.02
Elective/relative	183 (76.9%)	55 (23.1%)	
Absolute	12 (54.5%)	10 (45.5%)	

in the SPN group. Univariable analysis showed the following factors to impact WIT: tumor size, surgical approach, type of indication (Table 2). Intraoperative blood loss was significantly lower in the SE group (177 cc vs 221 cc, $p = 0.02$). Pathology results are reported in Table 3. In both groups most tumors were malignant with the clear cell form being the most frequent hystotype. Pathological stage was mainly pT1a. Significant differences emerged between the two groups in terms of presence of coagulative necrosis and PSM. The incidence of PSM was significantly lower in patients treated with SE compared to SPN (1.4% vs 6.9%; $p = 0.02$). Multivariable analysis demonstrated that the surgical technique was the only independent predictor of PSM (Table 4). The overall incidence of early medical and surgical complications was similar in both groups (42/198, 24%, in SPN vs. 37/198, 18.7%, in SE group; $p = $ n.s.). Medical complications were reported in 13/198 (6.6%) and 7/198 (3.5%) patients in the SPN and SE group, respectively ($p = $ n.s.). Surgical Clavien II complications were reported in 11 (5.6%) patients in the SPN and in 16 (8%) patients in the SE group ($p = $ n.s.) Surgical Clavien III complications were reported in 9 (8%) patients in the SPN and in 10 (5%) patients in the SE group ($p = $ n.s.). There were not Clavien grade IV and V complications.

Comments

Recently, the interest for NSS has increased as several studies have demonstrated the oncologic equivalence with radical nephrectomy (RN) for the treatment of T1 RCC.[14,15] Various NSS techniques have been described. In 1950, Vermooten first suggested that peripheral renal tumors could be locally excised by leaving a margin of healthy parenchyma around the tumor of at least 1 cm.[16,17] Further studies have demonstrated that surgical margin involvement does not necessarily indicate residual disease or adverse prognosis.[18] To date, there are no established recommendations regarding the optimal width of healthy surgical margin during NSS. The European Association of Urology (EAU) Guidelines recommend the presence of a minimal, but not better specified, tumor-free surgical margin surrounding the resected tumor.[19] In recent years, data has emerged demonstrating good oncologic, functional and perioperative outcomes of SE.[5,20,21] To our knowledge, this study represents the first multicenter clinical study comparing SE and standard PN in terms of intraoperative, early postoperative and pathological outcomes in patients with clinical T1 renal

Table 3
Pathological data.

	Standard PN	SE	P
Pathological size			
Mean (SD)	3.2 (1.3)	3.1 (1.2)	n.s.
≤4 cm n, (%)	158 (79.8%)	160 (80.8%)	n.s.
4.1–7 cm n, (%)	38 (19.2%)	37 (18.7%)	
>7 cm n, (%)	2 (1.0%)	1 (0.5%)	
Histotype			
Malignant n, (%)	145 (73.2%)	147 (74.2%)	n.s
Benign n, (%)	53 (26.8%)	51 (25.8%)	
Hystotype			
Clear cell n, (%)	103 (52%)	102 (51.5%)	n.s.
Papillary n, (%)	19 (9.6%)	28 (14.1%)	
Cromophobe n, (%)	20 (10.1%)	17 (8.6%)	
Not classified n, (%)	3 (1.5%)	0	
Oncocitome n, (%)	26 (13.1%)	26 (13.1%)	
Angiomyolipoma n, (%)	19 (9.6%)	16 (8.1%)	
Others (Benign) n, (%)	8 (4.1%)	9 (4.6%)	
PT stage			
pT1a n, (%)	112 (77.2%)	115 (78.2)	n.s.
pT1b n, (%)	27 (18.6%)	25 (17)	
pT2 n, (%)	2 (1.4%)	0	
pT3a n, (%)	4 (2.8%)	6 (4.1)	
pT3b n, (%)	0	1 (0.7%)	
Surgical margins			
Negative n, (%)	135 (93.1%)	145 (98.6%)	p = 0.02
Positive n, (%)	10 (6.9%)	2 (1.4%)	
Coagulative necrosis			
Absent n, (%)	123 (84.8%)	139 (94.6%)	p = 0.01
Present n, (%)	22 (15.2%)	8 (5.4%)	
Tumor grade			
1-2 n, (%)	112 (78.9%)	127 (86.4%)	n.s.
3-4 n, (%)	30 (21.1)	20 (13.6%)	
Sarcomatoid differentiation			
Absent n, (%)	144 (99.3%)	146 (99.3%)	n.s.
Present n, (%)	1 (0.7%)	1 (0.7%)	

Table 4
Univariate and multivariate analysis for positive surgical margins in 292 malignant tumors.

	Univariate analysis			Multivariate analysis for surgical margin		
	Negative surgical margins	Positive surgical margins	p	RR	95% CI	p
Age, mean (SD)	62.5 (12)	66.5 (7)	0.25	–	–	–
Tumor size (cm), mean (SD)	3.2 (1.3)	3.2 (1.5)	0.90	–	–	–
Tumor growth pattern, n. (%)			0.50	–	–	–
≥50% exophytic	209 (95.4%)	10 (4.6%)				
>50% endophytic	71 (97.3%)	2 (2.7%)				
Tumor location, n. (%)			0.21	–	–	–
Polar	164 (93.7%)	9 (6.3%)				
Mesorenal	116 (97.5%)	3 (2.5%)				
Symptoms at diagnosis, n. (%)			0.90	–	–	–
Symptomatic	43 (95.6%)	2 (4.4%)				
Asymptomatic	237 (96%)	10 (4%)				
Indication, n. (%)			0.03	3.1	0.70—13.68	0.14
Elective/Relative	259 (96.6%)	9 (3.4%)				
Absolute	21 (87.5%)	3 (12.5%)				
Surgical approach, n. (%)			0.25	–	–	–
VLP	90 (97.8%)	2 (2.2%)				
Open	190 (95%)	10 (5%)				
Surgical technique, n. (%)			0.02	4.7	1.00—22.45	0.050
SE	145 (98.6%)	2 (1.4%)				
PN	135 (93.1%)	10 (6.9%)				
PT stage n, (%)			0.90	–	–	–
pT1a	218 (96%)	9 (4%)				
pT1b	50 (96.1%)	2 (3.9%)				
pT2	2 (100%)	0				
pT3a	9 (90%)	1 (10%)				
pT3b	1 (100%)	0				
Tumor grade n, (%)			0.03	2.6	0.74—9.31	0.14
1—2 n, (%)	232 (97.1%)	7 (2.9%)				
3—4 n, (%)	45 (90%)	5 (10%)				
Coaugulative necrosis n, (%)			0.91	–	–	–
Absent	251 (95.8%)	11 (4.2%)				
Present	29 (96.7%)	1 (3.3%)				
Sarcomatoid differentiation n, (%)			0.77	–	–	–
Absent	278 (96.9%)	12 (3.1%)				
Present	2 (100%)	0				

tumors. The goal of NSS is reached when (1) WIT is low, (2) surgical margins are negative, and (3) no major complications are observed.[21] In the present series, the duration of ischemia was similar in both groups with mean ischemia time being <20 min. Mottrie et al. demonstrated that surgical experience, as well as the anatomic and pathologic characteristics of the treated tumors were independent predictors of WIT >20 min.[22] The results of a recent multicenter, international study confirmed previous data and demonstrated that anatomic aspects such as polar (superior/inferior vs. middle) and rim tumor (lateral vs. medial) location, the relationship between tumor and collecting system or renal sinus, and the exophytic rate of the tumor were able to predict WIT >20 min regardless of the clinical tumor size.[23] In this study, univariable analysis showed that tumor size, surgical approach and type of indications were associated with WIT >20 min. Overall, 46.7% of patients that underwent laparoscopic surgery and 13.5% of patients that underwent open

surgery had a WIT> 20 min. According to EAU Guidelines, open NSS currently remains the standard of care and laparoscopic NSS (LNSS) should be performed by experienced surgeons.[19] These results are in line with published data.[19] The achievement of negative surgical margins is one of the major challenges of NSS. PSM after NSS occurs in 2—8% of patients.[24] The presence of PSM as risk factor for disease recurrence after NSS is still a matter of debate, however, it should prompt more frequent and intensive surveillance.[25] The need to excise a rim of healthy parenchyma to avoid the risk of PSM and local recurrence is controversial. The incidence of PSMs in the present study is within the published ranges. Unexpectedly, in the present study the incidence of PSM was significantly lower in patients treated with SE and 4.7 higher in pts undergoing SPN. Moreover, results from multivariable analysis showed that surgical technique was the only independent predictor of PSM. Although the low PSM rate after SE is in accordance with previously published data,[5] this

finding of a protective effect on PSM of SE has to be considered very carefully, as many factors not included in the multivariable analysis could have influenced our results, including the different experience in SE or SPN of surgeons and pathologists involved in the different centers. Furthermore, although statistically significant, the lower incidence of PSM in the SE group is numerically very low (8pts), and might become even less significant in larger series. Nevertheless, present data should be regarded as a proof against a clear oncological superiority of SPN vs SE, that although expectable and intuitive, is far from being demonstrated. Several circumstances might promote the occurrence of a PSM, such as poor intraoperative visibility and orientation, and infiltrating tumor pattern.[26] Results from the present study could be also explained by the fact that during SE, a natural cleavage plane between the tumor pseudocapsule and the normal parenchyma is followed thus allowing for a blunt dissection without entering the tumor.[27,28] The oncologic safety of blunt tumor enucleation of RCC has been demonstrated by pathological studies which have described the presence of an inflammatory tissue with a median thickness of 1 mm which allow the presence of negative surgical margins also for tumors microscopically extending beyond the tumor capsule.[27] This thin layer of normal tissue is present as 'leopard spots' on the intact tumor capsule, and always presents in case of neoplastic penetration of the capsule into the kidney tissue.[27] NSS is technically more challenging than RN and therefore has a higher complication rate. Literature data concerning NSS morbidity are extremely variable and the overall complication rate ranges between 4% and 37%.[29] However, in the past decade, better patient selection, operating techniques, peri-operative care, and surgical experience allowed a reduction of complications.[27] Intraoperative blood loss is a relevant issue during NSS. Results from the present study demonstrate significantly lower operative times and intraoperative blood loss in patients treated with SE although this reduced bleeding was clinically not relevant. These results may be explained by the existence of a natural cleavage plane dissection plane between the tumor capsule and the normal parenchyma. Overall, the number of patients with complications in the present study was within the published ranges with similar early complication rate between the two groups. The incidence of surgical and medical complications did not differ significantly between SPN and SE. This study represents the first large multicenter, non randomized matched-pair analysis aiming to compare the perioperative outcomes of SE versus SPN in clinical T1 renal tumors. We acknowledge some limitations to the present study: the lack of randomization, the lack of nephrometric classification system and the lack of central pathologic review that did not allow the evaluation of the thickness of peritumoral tissue in either surgical procedure, with the aim of confirming histologically the kind of surgical procedure performed in each case; the type of surgical technique adopted was reviewed from each institutional database originated from copies of original operative reports. Moreover the choice of which NSS technique to perform was based on surgeon preference.

Conclusions

In a large multicenter prospectively derived dataset, SE is associated with shorter operative time and lower blood loss if compared to SPN. The two techniques are associated with similar WIT and similar incidence of overall, surgical and medical complications. The incidence of PSMs seems to be higher with SPN. The latter results need to be confirmed in further randomized studies aimed to minimize the possible confounding factors implied by a multicentre, observational study design.

Conflict of interest disclosure

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Abbreviations

NSS:
Nephron-Sparing Surgery.
RN: Radical Nephrectomy.
SPN:
Standard Partial Nephrectomy.
SE: Simple Enucleation.
RECORd:
The Italian Registry of Conservative Renal Surgery.
ECOG:
Eastern Cooperative Oncology Group.
WIT:
Warm Ischemia Time.
PSM:
Positive Surgical Margin.