

Partial Nephrectomies: Results of 12 Years from an Oncology Institution

Nefrectomias Parciais: Resultados de 12 anos numa Instituição Oncológica



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ABSTRACT

Introduction: The diagnosis of renal cell carcinoma has been increasing in recent years, especially due to incidental cases, and thus indication for nephron-preserving surgery has also risen.

Objectives: To review a series of partial nephrectomies from an oncology institution namely technique features, survival and change in renal function.

Material and Methods: A retrospective analysis of all patients with renal tumors that were submitted to partial nephrectomy at our institution between January 2000 and December 2012.

Results: A total 156 partial nephrectomies were performed, 85 in men and 71 in women, with mean overall age of 62 ± 15 years. Surgical approach was transperitoneal laparoscopic in 23 cases with the remainder 133 through lumbotomy. Mean ischemic time was < 25 min in all patients and complication rate was 10.9 %, mostly corresponding grade 2 and 3 of the Clavien-Dindo scale. Mean tumor size was 2.9 ± 1.4 cm and the surgical margin was focally affected by tumor in 9.6% of cases. Histologically, 26.2% of cases corresponded to clear cell renal cell carcinoma, with oncocytomas being the most common benign neoplasm with 14.7% of the total. There were 4 cases of recurrence and one case death at follow-up. The mean change in estimated glomerular filtration rate was -5.3 mL/min per 1.73 m^2 ($p < 0.001$). There was no association between warm ischemia time, body mass index, age, ASA score, presence of complications with this decrease in glomerular filtration rate.

Discussion: Our positive surgical margins cases were slightly above what is described in literature, however we didn't find any predictive factor for such finding and ultimately there was no evidence of tumor recurrence or influence in survival in all these cases. Even though there was a significant decrease in estimated glomerular filtration rate, warm ischemia time was very low and only five patients presented with *de novo* eGFR < 60 mL/min per 1.73 m^2 , and two patients started hemodialysis. A high volume center seems to be critical for technique optimization and complication management.

Conclusion: Our series of partial nephrectomies presents oncological results and preservation of renal function similar to those published in literature. This is a safe technique with good results, justifying its growth.

Keywords: Chronic Disease; Glomerular Filtration Rate; Nephrectomy; Renal Insufficiency.

RESUMO

Introdução: O diagnóstico de carcinoma de células renais tem vindo a aumentar nos últimos anos, sobretudo pelo seu diagnóstico incidental, e de forma paralela tem aumentado as indicações para cirurgia preservadora de nefrónios.

Objetivos: Rever uma série de nefrectomias parciais de uma instituição oncológica em termos técnicos, sobrevida, variação da função renal.

Material e Métodos: Análise retrospectiva de todos os doentes com neoplasia renal, submetidos a nefrectomia parcial na nossa instituição entre janeiro de 2000 e dezembro de 2012.

Resultados: Foram realizadas 156 nefrectomias parciais, 85 em homens e 71 em mulheres, com média de idades de 62 ± 15 anos. A abordagem foi em 23 casos transperitoneal laparoscópica sendo nos restantes 133 por lombotomia. O tempo médio de isquemia foi < 25 minutos em todos os doentes. A taxa de complicações foi de 10,9%, a maioria grau 2 e 3 da escala de Clavien-Dindo. Os tumores tinham dimensões médias de $2,9 \pm 1,4$ cm e a margem cirúrgica estava focalmente atingida por tumor em 9,6% dos casos. Em termos histológicos, verificou-se em 26,2% dos casos a existência de carcinoma de células renais de células claras, sendo os oncocitomas a neoplasia benigna mais frequente com 14,7% do total. No seguimento dos doentes verificaram-se 4 casos de recidiva e um óbito pela doença. A variação média na taxa de filtração glomerular estimada foi de $-5,3$ mL/min por $1,73 \text{ m}^2$ ($p < 0,001$). Não se verificou associação entre tempo de isquemia, índice de massa corporal, idade, score ASA, existência de complicações com este decréscimo da taxa de filtração glomerular.

Discussão: Os casos de margens cirúrgicas positivas são ligeiramente superiores ao descrito na literatura, todavia não foram encontrados fatores preditivos para tal e em última análise não foi encontrada recidiva tumoral ou qualquer influência na sobrevida destes doentes. Apesar de ter se ter verificado uma diminuição significativa da taxa de filtração glomerular, o tempo de isquemia quente foi muito reduzido e apenas cinco doentes apresentaram taxa de filtração glomerular *de novo* < 60 mL/min por $1,73 \text{ m}^2$ e apenas dois iniciaram programa regular de hemodiálise. Um centro de grande volume cirúrgico parece ser necessário para optimização técnica e resolução de complicações.

Conclusão: A série de nefrectomias parciais apresenta resultados de controlo oncológico e de preservação da função renal sobreponíveis aos de outras séries da literatura. Esta é uma técnica segura que apresenta bons resultados, justificando o seu crescimento.

Palavras-chave: Insuficiência Renal Crónica; Nefrectomia; Taxa de Filtração Glomerular.

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INTRODUCTION

Renal cell carcinoma (RCC) represents about 3% of all malignancies and it is the third most common cancer in the urinary tract. In 2012 there were 84 400 new cases and a total of 34 700 deaths from kidney cancer in Europe.^{1,2}

The diagnosis of renal cell carcinoma has been rising, not only from the widespread use of imagiologic exams but also from technical refinements of these, allowing better diagnostic accuracy.

In the early 1970s, the incidental detection rate was reported as 7% - 13%, but this percentage has increased to 48% - 66% in recent years. Concomitantly there has been a shift towards the detection of small tumors in asymptomatic patients and ultimately in lower stages.^{3,4}

Although there is some controversy on the true values of mortality rate of RCC, it seems that mortality rates are decreasing.^{5,6}

Currently the cornerstone treatment of T1a tumors is partial nephrectomy (PN), and this is supported in the European Association of Urology Guidelines on Renal Cell Carcinoma albeit nephron-sparing surgery is indicated for tumors up to 7 cm diameter, whenever technically feasible.^{7,8}

Long-term studies have shown that PN has oncological outcomes comparable to those obtained after radical nephrectomy (RN), while reducing the risk of *de novo* chronic kidney disease (CKD).⁹

In a large community-based study, chronic kidney disease was found to be an independent risk factor for the development of cardiovascular events (coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease), hospitalization and even death.¹⁰

The cellular mechanism by which a reduced estimated glomerular filtration rate (eGFR) affects the cardiovascular system is not yet elucidated.

This way, cardiovascular complications from CKD seem to be reduced after PN, even though there are still some patients that suffer a decline in renal function.¹¹

Retrospective multi-institutional studies showed a trend towards a benefit of survival in patients submitted to PN when comparing to RN, although a recent prospective study brings conflicting evidence around this subject. In the only randomized trial of RN versus nephron-sparing surgery (NSS), it was concluded that NSS substantially reduced the incidence of at least moderate renal dysfunction (eGFR < 60), while the incidence of advanced kidney disease (eGFR < 30) and kidney failure (eGFR < 15) was relatively similar in the two treatment arms. They further add that the beneficial impact of NSS on eGFR did not result in improved survival over a period of 9,3 years of follow-up.¹²⁻¹⁴

Primary objective of this study was to characterize a series of PN over a period of more than 10 years from an oncological institution, namely technique and oncological outcomes. A secondary goal is to review the effects of this surgical technique in renal function and the analysis of predictive factors of this variation.

MATERIAL AND METHODS

We performed a retrospective analysis of all patients submitted to PN in the urology department of an oncological institution from January 2000 until December 2012.

All patients had a computed tomography (CT) or a magnetic resonance imaging (MRI) confirming the existence of a renal mass suspicious of RCC that was evaluated by a team of 2 urologists that decided eligibility to perform a PN. Noteworthy there were 10 cases of suspected angiomyolipoma on CT imaging, which were purposed for surgery taking into account one of these situations: young females in childbearing age and tumors larger than 4 cm with patients prone to NSS.

R.E.N.A.L nephrometry score was calculated based on the anatomical features of renal tumors according to its specific protocol.¹⁵

Even though our series starts in 2000, the American Joint Committee on Cancer 2010 TNM classification was used to assign the RCC stage for our cohort to obtain uniformity.^{16,17}

Anesthesiology evaluation prior to surgery was mandatory. All patients completed serum analysis with hemogram, biochemistry and coagulation study, chest x-ray and electrocardiogram, one month before surgery.

Estimated GFR was calculated using the Modification of Diet in Renal Disease equation based on serum creatinine one month before surgery and 6 months after surgery.¹⁸

All patients were submitted to general anesthesia and had antibiotics prophylaxis with a single dose of cefazolin (except for allergic to beta-lactam antibiotics), as well as venous thromboembolism prophylaxis with low molecular weight heparin.

Open partial nephrectomy (OPN) was performed through a flank incision with tumor excision under warm ischemia or clampless and renorrhaphy was performed with an absorbable suture. Laparoscopic partial nephrectomy (LPN) was performed through a transperitoneal approach and renorrhaphy was performed with V-Loc® suture (Covidien, Ireland).

Both in OPN and LPN a Surgicel® mesh (Ethicon, a Johnson and Johnson Company, Somerville, NJ) and Floseal® (Baxter Healthcare Corporation, Deerfield, IL) were applied within tumor excision site.

Complications were described using the modified Clavien-Dindo classification scale.¹⁹

Statistical analysis was performed for sample description. The median values presented in the results are followed by the semi-quartile range (SQR) given by (P75-P25)/2. Comparisons in eGFR and Hb levels before and after surgery were performed using the Wilcoxon non-parametric test. Oncological outcomes were analyzed comparing different surgical approaches, tumor size and nephrometry score with surgical margins status and complications.

Predictive factors for renal function variation were tested using linear regression models. Disease free survival function was estimated using Kaplan-Meier estimator.

All analyses were performed using SPSS® version 18.0

(IBM Corp., Armonk, NY, USA).

RESULTS

A total 156 PN were performed in the period of analysis. Patient demographics, technique, hospitalization and tumor characteristics are presented in Table 1.

There was a slight predominance of male gender accounting for 54.5% of the cases (n = 85). Mean age was 61.6 ± 14.8 years and mean body mass index (BMI) was 25.1 ± 3.9 kg/m².

The number of surgeries increased gradually from 2000 to 2012, with a maximum of 37 partial nephrectomies in 2012 (Fig. 1).

In the majority of cases (89.1%) the diagnosis was incidental in asymptomatic patients while six cases presented lumbar pain and 8 cases with hematuria.

Indication for surgery was mainly elective. Eight cases were performed in solitary kidneys and three cases corresponded to synchronous bilateral tumors.

There were 15 patients with relative indication (this includes patients with severe cases of diabetes and hypertension of difficult control).

Surgical technique and perioperative outcomes

When one analyses surgical parameters, open surgery with lumbotomy approach was the preferable technique and accounted for 133 cases (85.3%) while transperitoneal laparoscopy represented 23 cases (14.7%).

Average surgical time was 81.2 ± 20.1 minutes and warm ischemia time (WIT) was lower than 25 minutes for the whole cohort, with 12 patients with clampless procedure. Median blood loss was 100 ml (range 150) whilst median drop in post-operative hemoglobin was 1.5 mg/dL with a maximum drop of 5.9 mg/dL (p < 0.001 - Wilcoxon test).

Table 1 - Patient demographics, technique, hospitalization and tumor characteristics

Variable	Value ± SD (% or min; max)
Sex	
Male	85 (54.5%)
Female	71 (45.5%)
Age (years)	61.6 ± 14.8
Body mass index (kg/m ²)	25.1 ± 3.9
Median ASA	2
Median hospitalization (days)	5 (3;28)
Surgical approach	
Lumbotomy	133 (85.3%)
Laparoscopy	23 (14.7%)
Mean surgical time (minutes)	81.2 ± 20.1 (50;130)
Median blood loss (ml)	100 (0;1500)
Mean ischemia time (minutes)	10.7 ± 7.6 (0;25)
Mean tumor dimensions (cm)	2.9 ± 1.4 (1.2;13)
Mean RENAL score	5.1 ± 1,1 (4.0;8.0)
Side	
Left	75 (48.1%)
Right	81 (51.9%)

ASA: American Society of Anesthesiologists; SD: standard deviation.

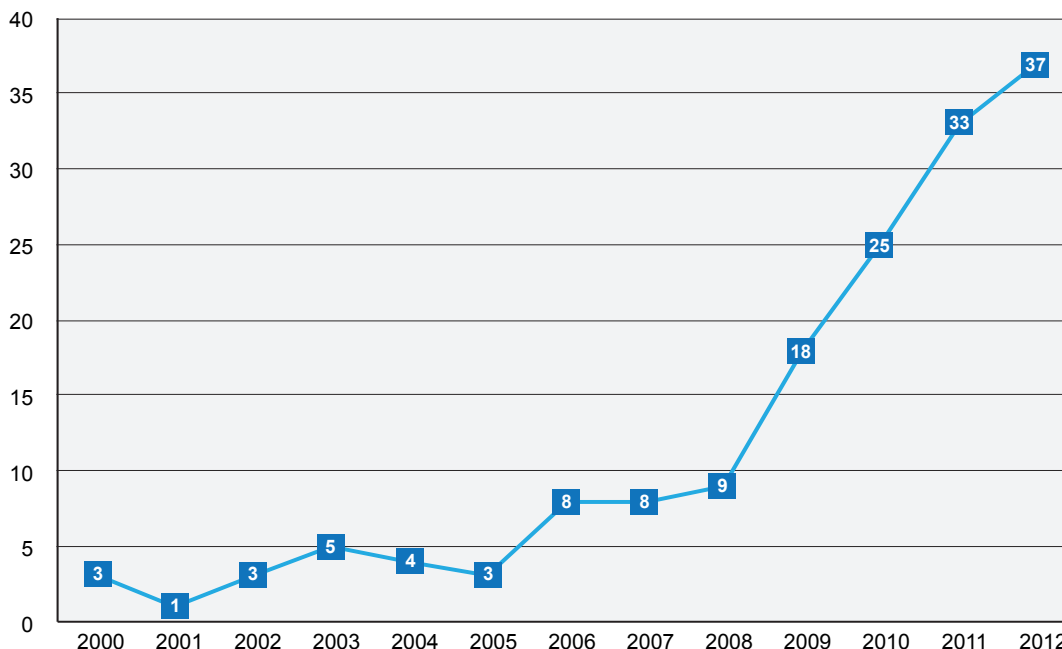


Figure 1 - Number of surgeries per year (n)

As for complications, the overall complication rate was 10.9% with the majority of cases corresponding to grade 2 and 3 of the Clavien-Dindo scale. There was a single case of perioperative mortality (0.6%). No significant predictors of complications were found in univariate analysis ($p > 0.05$).

There were 2 cases of early total nephrectomies, one due to renal abscess and one due to an expanding hematoma. The median hospital stay was 5 days, and there was need for readmission in 5 cases (3%). Surgical complications are described in Table 2.

Table 2 - Complication description according to Clavien-Dindo scale

Complication	Clavien-Dindo scale degree	n
Surgical wound infection	II	2
Acute pyelonephritis	II	1
Nosocomial pneumonia	II	1
Retroperitoneal hematoma	I/II	2
Pseudoaneurism	IIIb	3
Urinary fistula	IIIb	1
Hematuria - bladder clot	IIIb	1
Abscess (nephrectomy)	IIIb	1
Perirenal hematoma	IIIb	2
Septic shock	IVa	2
Septic shock	V	1

Oncological outcomes

Mean tumor size was 2.9 ± 1.4 cm and the surgical margin was focally affected by tumor in 9.6% of cases. Average RENAL nephrometry score was 5.1 ± 1.1 with a maximum of 8.0. The majority of cases were included in low risk group category ($n = 106$) with no high risk tumors in this case series.

The results of histology and pathological staging are presented in Fig.s 2 and 3 respectively.

Renal cell carcinoma (RCC) was the most frequent tumor in histological exam, with 26,6% of clear cell RCC, 16,7% chromophobe RCC and 12,8% papillary RCC of total tumors. When analyzing benign tumors, oncocytomas and angiomyolipomas represented 14,7% and 8,3% of the total respectively. There were 5 cases of simple cyst, one RCC that couldn't be classified, one multilocular cystic RCC and one metanephric adenoma.

When categorizing malignancy cases, 97 corresponded to a pT1a stage, and most notably 7 cases of stage pT3a (Fig. 4)

Overall there were 4 recurrence cases in maximum follow-up of 84 months, and margin status was negative for all cases ($p > 0.05$).

One patient (pT1a clear cell RCC with sarcomatoid differentiation, Fuhrman 4) that presented metastatic disease on follow-up, died after 36 months of follow-up. Another patient at 12 months follow-up presented a lesion in contralateral kidney for which he was submitted to percutaneous cryoablation (standard biopsy confirmed clear cell RCC). Two patients have a probable RCC lesion

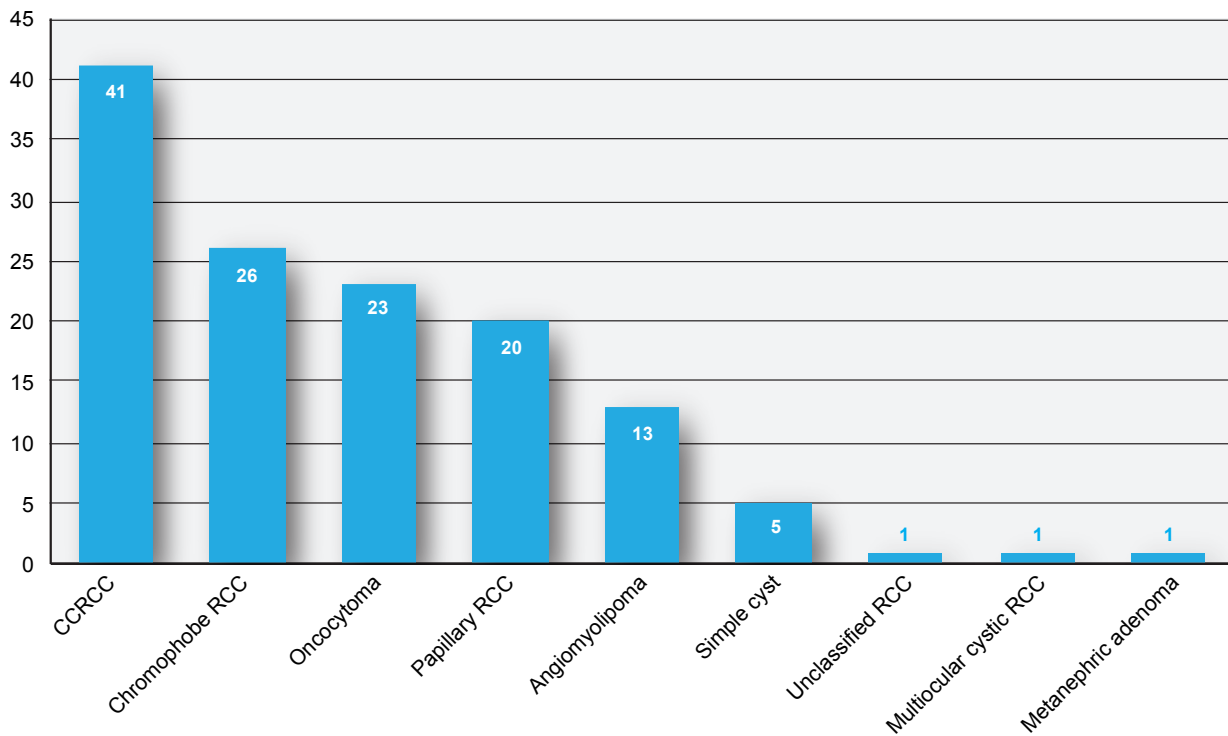


Figure 2 - Histology results.

CCRCC: clear cell renal cell carcinoma; RCC: renal cell carcinoma

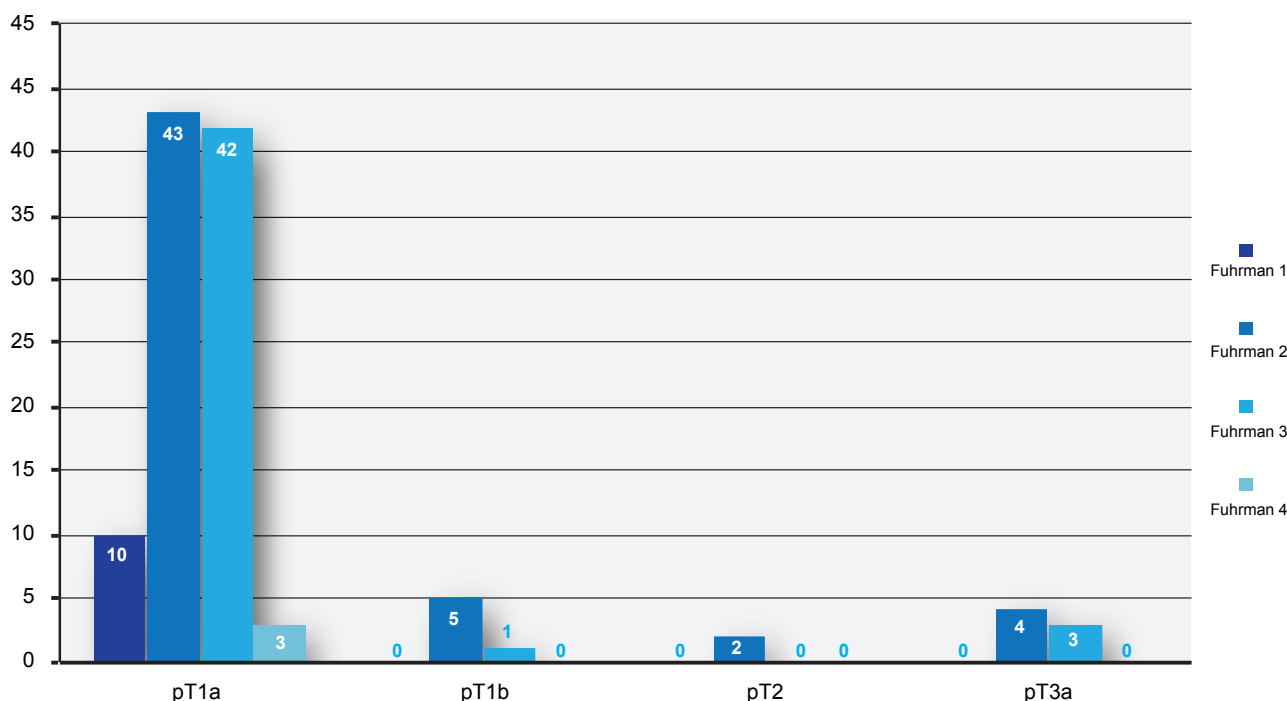


Figure 3 - T Staging and Fuhrman Grade

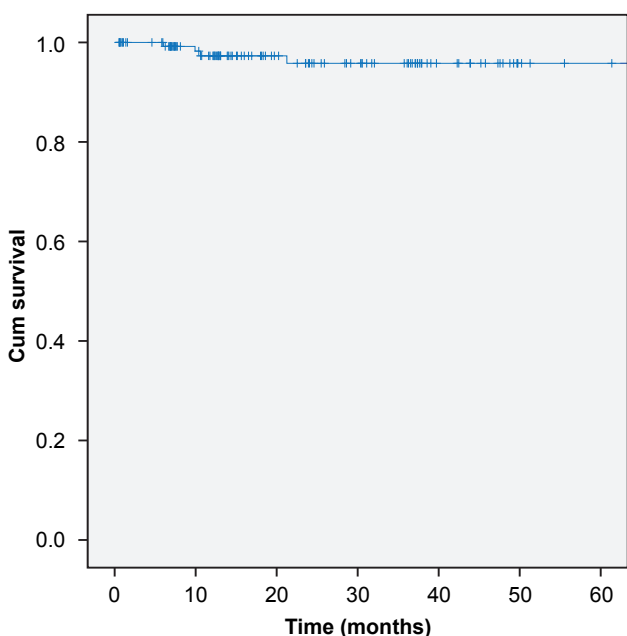


Figure 4 - Disease-free survival (Kaplan-Meier analysis)

in ipsilateral kidney, which are currently under imagiologic surveillance.

There was one death due to metastatic disease from another neoplasm (already know endometrial tumor). There was a single case of loss to follow-up. All other were free of disease at last follow-up with a median follow-up of 22 months (min 4 and max 84 months).

Statistical analysis was performed to assess predictors of margin status. However neither surgical approach

($p = 0.2$ Fischer test), nor tumor size ($p = 0.9$ Mann-Whitney test) seemed to be associated with positive margins. Similarly, there was no association between risk groups of RENAL score and margin status ($p = 0.4$).

Effects on renal function

Renal function results are presented in Table 3. There were no patients in hemodialysis prior to surgery.

We obtained a median post-operative eGFR of 73.0 (11.5) ml/min per 1.73 m² and a median change in eGFR of -3.9 (5.7) mL/min per 1.73 m². There were significant differences between the level of eGFR post-surgery and the level of eGFR pre-surgery ($p < 0.001$). Even though we analyzed predictive factors that could affect this renal variation, none of them, including WIT, BMI, ASA score, age, presence of complications, tumor size and RENAL score was statistically significant ($p > 0.05$). We conducted subgroup analysis for the particular case of patients with previous diagnosis of severe diabetes and hypertension of difficult control, but similarly there was no relationship with eGFR variation ($p = 0.4$).

Curiously laparoscopic approach was associated with a lower variation in eGFR, when compared with open approach. ($p = 0.01$).

We had only five cases of the *de novo* eGFR < 60 mL/min per 1.73 m² at last follow-up, and only two cases that needed hemodialysis.

One case that started a regular program of hemodialysis had a solitary kidney and previous eGFR < 30 ml/min per 1.73 m², while the other patient had previously diagnosed diabetic nephropathy, also with previous eGFR < 30 ml/min per 1.73 m².

Table 3 - Renal function results: estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease

Variable	Value
Median (SQR) preoperative eGFR	75.3 (11.5) min 19.2; max 182.5
Median (SQR) eGFR at 6 months post-op	73.0 (11.5) min 14.6; max 147.9
Median (SQR) eGFR change	-3.9 (5.7)
Preoperative eGFR < 60 ml/min/1.73 m ² - n	25 (16.0%)
eGFR < 60 at last follow-up - n	30 (19.2%)
<i>de novo</i> eGFR < 60 ml/min/1.73 m ² at last follow-up - n	5 (3.2%)
Patients in hemodialysis - n	2 (1.3%)

eGFR: estimated glomerular filtration rate in ml/min/1.73m²; SQR: semi-quartile range

DISCUSSION

PN has become standard care for T1a RCC and one must consider this approach for T1b cases whenever technically feasible.^{7,20}

This work translates the continuous growth of this technique in an oncologic institution. We presented a 9.6% cases for positive surgical margin (PSM), which is slightly above what is described in literature, ranging from 0% - 7%.²¹

However when looking for solitary kidneys case series, PSM can achieve 15% - 16.6%.^{22,23} Most of our PSM were referred to first LPN experience between 2002 and 2008, accounting for 10 of 15 total cases. This approach is known for its difficult learning curve and in our case included three cases in solitary kidneys.^{23,24}

Moreover when we analyzed predictors for PSM, no tumor size, RENAL score nor surgical approach seemed to condition margin status.

With only one case of death due RCC, the main goal of cancer specific survival above 95% was achieved.²⁵ In a period of two year of follow-up with a surveillance strategy, there was no evidence of tumor recurrence or influence in survival in all cases of PSM.²⁶

In a recent study, Yossepowitch et al studied the pathologic features of 1 390 patients who underwent NSS finding a global rate of PSMs of 5.5%, with decreasing tumor size and presence of a solitary kidney being predictors of positive surgical margins. The overall 10-year probability of freedom from local disease recurrence was 93% and from metastatic progression 93%, with no significant difference between patients with positive margins when compared to those with negative margins. Authors stated that PSM do not uniformly portend an adverse prognosis and further add that while every effort should be taken to ensure clear margins, surveillance for those with PSM doesn't seem to compromise long-term disease-free survival.²⁷

These data were further supported in a 2013 review that stated that considering the low risk of local recurrence, development of metastasis, or cancer-specific mortality, careful surveillance could be the best management option for most patients with PSM after NSS.²¹

We had an overall complication rate of 10,9%, the majority of which Grade 2 or 3 of the Clavien-Dindo surgical scale and therefore within what is described in literature (complication rates between 6% and 20%). Post-operative mortality is also low with only one case due to septic shock.^{6,28}

Tumor size in our series is also worth mentioning; with an average of 2.9 cm it also includes 30 cases with more than 4 cm. One anecdotal case refers to a tumor with 13 cm corresponding to an angiomyolipoma that was feasible to extract. These particular cases correspond to 6 of the cases with PSM, and thus can also justify the slightly higher PSM casuistic. The seven cases of pT3a correspond to tumors that invaded the perirenal fat.

Our series included 23 oncocytomas, 13 angiomyolipomas, 5 simple cysts and 1 metanephric adenoma which in overall corresponds to a total 27% of benign tumors. However one must take in account specific considerations about majority of these tumors. The 23 oncocytomas all corresponded to contrast enhanced suspicious lesions on CT and the same happened with the simple cysts, all of which graded as Bosniak III. The overall percentage of benign tumors in our series includes previously known angiomyolipomas on CT/MRI exams (n = 10) that fulfill criteria for PN.

These data seem to provide more arguments about the importance of NSS.

Although the exact threshold of warm ischemia beyond which irreversible kidney injury occurs is controversial, contemporary data suggest aiming below 20 – 25 min. In fact with a warm ischemia time of 10.7 minutes and 12 clampless procedures, our series achieved lower values than others stated in literature.²⁹

Beside there was a statistically significant decrease in eGFR post PN, few patients (n = 5) presented with *de novo* eGFR < 60 ml/min per 1.73 m² after surgery and a low number of patients started hemodialysis. In fact, the lack of association with predictive factors such as WIT may point out to other factors to justify these particular cases such as underdiagnosed baseline pathologies like diabetes or hypertension. We obtained a significant association on

univariate analysis between laparoscopic approach and lower decrease in eGFR, which may be correlated with patient selection for this technique (fitter patients with low BMI).

While the impact of a nephron sparing surgery (NSS) on overall survival is being discussed with the results of the EORTC randomized trial 30904, its effect on renal function has been well established for at least moderate renal dysfunction (eGFR < 60 ml/min per 1.73 m²) providing better results than RN.^{14,30}

In 2012, Kim et al published a meta-analysis in which partial nephrectomy showed a survival advantage and a lower risk of severe chronic kidney disease, and this is emphasized in the latest edition of European Urology Guidelines on RCC.^{7:31}

In retrospective series Huang et al obtained a 3-year probability of freedom from new onset of eGFR lower than 60 mL/min per 1.73 m² of 80% after partial nephrectomy and 35% after radical nephrectomy ($p < 0.0001$). In their study radical nephrectomy remained an independent risk factor for patients developing new onset of GFR lower than 60 mL/min per 1.73 m².³²

A matched comparison of PN and RN from the Mayo Clinic has shown a higher risk for proteinuria and chronic renal insufficiency after RN (risk ratio: 3.7).³³

It seems that in the long-term patients submitted to RN will be in jeopardy not only for CKD but also for all the possible risks associated with it, namely cardiovascular morbidity and risks of hospitalization.

Ultimately NSS can lead to better quality of life, by diminishing such concerns.³⁴

A high volume center seems to be critical for optimizing

technique towards oncological and functional success, and for complications management.³⁵

Limitations of the present study include its retrospective bias, and a low number of patients with a follow-up longer than 5 years.

CONCLUSION

There is a trend towards nephron sparing surgery in RCC, and this is the reality in our institution. Even though the slightly higher PSM than stated in literature, oncological outcomes have not been compromised. In fact PN proved to be a safe technique not only oncologically but also in terms of overall complications.

With low ischemia times and a low impact on renal function, this is a technique in continuous growth.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patient's data publication.

CONFLICTS OF INTEREST

The authors state no conflict of interests and have received no payment to perform this work.

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