

Laparoscopic Versus Open Partial Nephrectomy for Stage T1a of Renal Tumors

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Purpose: Partial nephrectomy is the gold standard treatment for small kidney masses. Data on the comparison of laparoscopic (LPN) versus open partial nephrectomy (OPN) are based on retrospective studies. Thus, we planned to compare these two techniques in a prospective trial.

Materials and Methods: The study population consisted of patients over 18 years old with single renal mass of ≤ 4 cm. Patients were divided into two groups considering their preference. Study arms were matched according to age, gender, tumor size and location and renal nephrometry score. Mean operation time, warm ischemia time, hospital stay, peri-operative complications and changes in glomerular filtration rate (GFR) after 1 month were recorded and compared in two groups. Patients' satisfaction score, visual analogue scale and narcotics use to control post-operative pain were also studied.

Results: 34 and 31 patients underwent LPN and OPN, respectively. There was no significant difference between OPN and LPN regarding hospital stay (4.1 versus 4.6 days; $P = .37$), mean hemoglobin drop (2.17 and 1.96 g/dL; $P = .62$), changes in GFR and positive margin (1 versus 3 $p = .40$). LPN was accompanied with longer mean surgery time (180 min versus 127 minutes; $P < .001$) and higher rate of urologic complications ($P = .04$); nevertheless, patient satisfaction rate was higher ($P = .02$) and dose of narcotics necessary for controlling post-operative pain was lower ($P = .04$) in LPN.

Conclusion: This clinical trial shows that LPN has some benefits over OPN, including decreased post-operative pain and higher patient satisfaction. However, extra caution should be considered in the issue of tumor margin and urinary leakage in LPN.

Key words: kidney neoplasms; laparoscopy; nephron sparing surgery; open partial nephrectomy.

INTRODUCTION

Nephron sparing surgery (NSS) was initially recommended for renal tumors in a solitary kidney, familial and multifocal masses and for those who already suffered from chronic kidney disease.⁽¹⁾ As time elapsed, further studies revealed that radical nephrectomy is a risk factor for chronic kidney disease; and saving as much renal parenchyma as possible would prevent subsequent kidney disease and related morbidities⁽²⁾. NSS provides effective long term benefits in localized renal tumors in terms of cancer control and renal function, and thus it is currently the standard treatment for renal masses under 7 cm (stage T1)^(3,4). Conversely, based on the evolution and increasing expertise in the field of minimally invasive surgery, a trend towards laparoscopic partial nephrectomy (LPN) in the treatment of small kidney masses has been developing^(5,6). Those who pioneered the field of LPN, applied it for relatively small and peripheral renal tumors⁽⁷⁾. Lower blood loss, post-operative pain, and shorter convalescence period alongside small incisions, have been confirmed as the primary advantages of LPN⁽⁸⁾. However,

there may be some concerns regarding the feasibility, safety, warm ischemia time (WIT), long-term changes in renal function and cancer control after LPN⁽⁵⁾. Open partial nephrectomy (OPN) was considered as the gold standard treatment for stage T1a of renal tumors for years⁽⁹⁾. Several studies has shown similar outcomes for LPN as compared to OPN⁽¹⁰⁾. Nevertheless, the main concern is that the majority of previous studies in this field are retrospective and there is a paucity of prospective clinical trials. The current study is the first clinical trial to compare the safety, side effects, changes in renal function and post-operative pain control between LPN and OPN in stage T1a of renal tumors.

MATERIALS AND METHODS

This study involves a non-randomized prospective trial that was carried out from September 2013 to December 2014 in two medical centers in Tehran, Iran. The sample size was calculated according to a pilot study to assess the difference in patient's satisfaction. Considering 95% confidence interval and 80% power for the study, a total of 60 patients were needed to achieve the

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Received June 2016 & Accepted November 2016

Table 1. Basic characteristics of the study population.

VARIABLE	OPN	LPN	TOTAL	P VALUE	
MEAN AGE, YEARS	54.8	50.3	52.4	0.20	
GENDER	Male	23	23	46 (70.8%)	0.30
	Female	8	11	19 (29.2%)	
BMI	27.4	26.9	27.1	0.50	
HISTORY OF SMOKING	9 (29%)	5 (14.7%)	14 (21.5%)	0.16	
CHIEF COMPLAINT	Incidental	12	21	33 (50.7%)	
	Flank pain	14	11	25 (38.4%)	
	Hematuria	4	2	6 (9.3%)	
	Others	1	0	1(1.6)	
MEAN TUMOR SIZE, MM	37.1	33.8	35.4	0.30	
TUMOR ETHNICITY	Exophytic	22	23	45 (69.2%)	0.60
	Endophytic	9	11	20 (30.8%)	
TUMOR LOCATION	Upper Pole	11	9	20 (30.8%)	0.70
	Mid Pole	7	10	17 (26.1%)	
	Lower Pole	13	15	28 (43.1%)	
RENAL NEPHROMETRY SCORE	5.87	5.81	5.84	0.80	

Abbreviations: OPN: open partial nephrectomy; LPN: Laparoscopic partial nephrectomy; BMI: Body mass index.

primary aim of the study, which was to compare the ratio of the side effects, patients' satisfaction and changes in renal function between LPN and OPN. All stages of the study were carried out under the supervision and approval of the ethical committee of the Iranian Urology and Nephrology Research Center. Written informed consent was presented to and taken from all patients. The study population included patients of over 18 years old with a single renal mass staged T1aNOM0 based on clinical and radiologic examinations. Exclusion criteria consisted of glomerular filtration rate (GFR) < 60 cc/min, masses in anatomically or functionally single

kidneys, inability to perform partial nephrectomy (such as a tumor in the hilar region) and absolute contra-indication for laparoscopy (bowel obstruction, infection of abdominal wall and aneurysm of great vessels). The study arms were not randomized due to patients' preference; Nevertheless, they were matched considering age distribution, gender, American Society of Anesthesiologists (ASA) classification for health status, tumor size and location (exophytic or endophytic, upper or mid or lower pole) and renal nephrometry score.

Surgical technique

LPN was performed under general anesthesia in lateral decubitus position. A 12 mm port was inserted at the umbilicus using open access approach. Then a 5 mm (sub xiphoid), 10 mm (para rectal region parallel to umbilicus), and 5 mm (2 cm medial to anterior superior iliac spine) ports were inserted under direct vision. For right sided operations, the 10 mm port was placed in sub xiphoid. Whenever necessary, another 5 mm port was used for liver retraction in the patients with right kidney mass. All patients underwent LPN via a transperitoneal approach. After medial mobilization of the colon and exposure of renal vascular pedicle, main renal artery was clamped using a bulldog. No cooling mechanism was used. The tumor was resected with a safe margin and extracted using an endobag. Renal parenchyma was sutured using a 2-0 absorbable polyglactine suture in a running fashion in one layer and bolster was not used routinely. For OPN, a flank incision was made in the same position. 11th or 12th rib was resected as required. Retroperitoneal approach was used to gain access to the kidney. Like LPN, only renal artery was clamped

Table 2. Frequency of post-operative complications in two groups.

Complication	LPN	OPN
Urinary Leakage	5	0
Sepsis	2	0
Delayed Hemorrhage	1	0
Abcess Formation	1	0
Azothemia	0	1
CVA	0	1
PTE	1	0
GI Bleeding	0	1
Overall	10(29%)	3(9.7%)

Abbreviations: LPN: Laparoscopic partial nephrectomy; OPN: Open partial nephrectomy; CVA: cerebro-vascular accident; PTE: pulmonary thromboemboli; GI: gastro-intestinal.

Table 3. Mean creatinine and GFR changes 1 day and 1 month after the surgery.

Variable	OPN	LPN	P value
Mean Cr changes after 24 hours (mg/dL)	+0.266	+0.084	0.002*
Mean Cr changes after 1 month (mg/dL)	+0.177	+0.097	0.115
Mean GFR changes after 24 hours (mL/min)	-14.34	-3.61	0.045*
Mean GFR changes after 1 month(mL/min)	-10.48	-8.56	0.572

Abbreviations: Cr, creatinine; GFR, glomerular filtration rate; OPN, open partial nephrectomy; LPN, laparoscopic partial nephrectomy.

and no cooling mechanism was used. Following control of small blood vessels with 8-figure knots and repairing the pyelocalyceal system, renorrhaphy was performed the same as laparoscopic approach. Whenever there were signs of urinary leakage (fever, flank pain, prolonged ileus and urinary discharge from drain), a double-j (Dj) stent was inserted via cystoscopy, and Foley catheter was kept until termination of urinary leakage. Otherwise, Foley catheter was withdrawn the day after surgery and percutaneous drain was removed when its daily output reached lower than 25 cc. Patients were subsequently discharged if there was no major complication.

Variables and statistics

Complications during surgery and after operation were listed and categorized according to Clavien-dindo classification. Warm ischemia time (WIT), operation time and hospital stay were recorded in all patients. To compute peri-operative bleeding, hemoglobin (Hb) changes, blood transfusion rate and estimated intra-operative hemorrhage (according to suction bottle) were used. Serum creatinine (Cr) and glomerular filtration rate (GFR) was measured before, one day and one month after surgery. Post-operative pain was assessed at the time of discharge using visual analogue scale (VAS). VAS has a score ranging from 0 to 10 in which 0 means no pain and 10 represents the worst possible pain. To control post-operative pain and discomfort, oral or rectal non-steroidal inflammatory drugs (NSAID) were given to the patient. In those patients whose pain did not respond to NSAIDs, intravenous pethidine (0.25 mg/kg) was injected. The total dosage of pethidine administered to control post-operative pain was measured in the first 24 hours after the operation and compared in the two study groups. To assess patient satisfaction score after one month, all patients were asked if they were satisfied with the operation; and what type of operation (open or laparoscopy) they would choose if they had the same surgery. SPSS version 18 was used for data analysis. Independent sample T-test and chi-squared test were used to compare variables and ratios between the two groups. P value lower than 0.05 was considered statistically significant.

RESULTS

Baseline Variables

In this study, 31 and 34 patients underwent OPN and LPN, respectively. The mean age was 54.8 and 50.3 years in OPN and LPN, respectively ($P = .20$). **Table 1** illustrates gender distribution, body mass index (BMI), patients' symptoms, tumor size, location and mean renal nephrometry score in the two groups. The mean tumor size was 37.1 and 33.8 mm

in OPN and LPN groups, respectively ($P = .30$). Mean operation time was significantly higher in LPN than OPN (180 versus 127 minutes, respectively, $P < .001$). There was no significant difference between the two groups regarding hospital stay (4.1 versus 4.6 days for OPN and LPN, respectively; $P = .38$). Mean hemoglobin drop one day after surgery was 2.17 and 1.96 g/dL in OPN and LPN groups, respectively; which was not statistically significant ($P = .62$). The mean packed red blood cell transfusion was lower in LPN than in the OPN group (0.55 versus 0.41 units), but was not statistically significant ($P = .52$). Estimated blood loss during the operation was measured using suction bottle at the end of surgery, which revealed no significant difference between the two groups (324 ml versus 310 ml for OPN and LPN groups respectively; $P = .80$). Peri-operative complications and intra-operative events: Eight out of 31 patients (25.8%) in OPN group suffered from pleural injury during the surgery, which was sutured and managed using a chest tube. Two cases in LPN were converted to open surgery, one of them was due to the injury on renal vein branches. None of the cases in either groups was converted to radical nephrectomy. No cases of bowel or visceral injury was observed. Any episode of high body temperature (over 38.5 ° Celsius) during hospital admission and after surgery was recorded. Although fever was more common among those who had undergone LPN (44% versus 19%), the difference was not statistically significant ($P = .09$). Post-operative complications are shown in **Table 2**. There were only 3 complications associated with OPN: 1 cerebrovascular accident, 1 gastrointestinal bleeding and 1 case of azotemia. Except for the latter, there was no other urologic complication. However, in LPN group, there were 5 cases of urinary extravasation (later treated with Dj insertion), 2 cases of urosepsis and 1 case of delayed hematuria (which was treated by expectant management). The relative frequency of urologic complications was significantly higher in the LPN group ($P = .04$). Positive margin was seen in 3 laparoscopic and 1 open case (8.8% and 3.2% respectively). Statistical analysis by Fisher's Exact Test did not show significant difference between the two groups ($P = .40$). There was no statistically significant relationship between positive margin and tumor size, location, tumor side and blood loss ($P = .50, .20, .60$ and $.90$ respectively). Changes in clearance of creatinine: There was an overall increase in mean serum creatinine 24 hours and one month after surgery. The mean changes of serum Cr was significantly higher after OPN than LPN one day after the operation (+0.266 mg/dL versus +0.084 respectively; $P = .002$). However, after one month, this difference was not statistically significant (+0.177 versus +0.097;

$P = .11$). As shown in **Table 3**, changes in mean GFR follow the same rule. The mean warm ischemic time (WIT) was 19.08 minutes in OPN and 20.97 minutes in LPN, which was not significantly different ($P = .50$). Post-operative pain control and patient satisfaction: Lower doses of pethidine was needed in LPN group to control patients' pain in the first 24 hours (16.3 mg versus 27.3 mg pethidine for LPN and OPN respectively; $P = .04$). However, evaluation of mean visual analogue scale (VAS) indicated no significant difference between the two groups ($P = .70$ and $P = .35$ for VAS before and after narcotic administration respectively). Further analysis of patient satisfaction (one month later) indicated that patients in the LPN group were more satisfied with the whole operation than those in the OPN group ($P = .02$).

DISCUSSION

Current information in the literature on the comparison of LPN and OPN in small renal masses are mainly based on retrospective articles and reviews. This study is the first prospective trial in which safety and efficacy of LPN and OPN are compared in pathological stage T1a of renal tumors⁽¹¹⁾. Historically, LPN was primarily used for relatively small, peripheral and exophytic kidney masses and retrospective studies were accompanied with a selection bias⁽⁷⁾; but in this study, endophytic and mid pole tumors were also included and matched in two comparative groups and renal nephrometry score which indicates surgical difficulty, is also similar in two groups. Patients' performance status and BMI were also matched in two groups. Thus this study tried involving a broader spectrum of renal masses in LPN group in order to achieve a more comprehensive conclusion. Furthermore, current data on advantages and disadvantages of LPN are complex and controversial. As a minimally invasive approach, it brings out small scar formation and more appealing appearance⁽¹²⁾. A study by Gill et al. revealed that LPN was accompanied with less intra-operative hemorrhage, earlier hospital discharge, rapid convalescence, and shorter surgery time. WIT was longer in LPN group, though. Like our study, the margin positive cases were higher in laparoscopic than open group (3 versus zero cases), although the difference was not significant ($P = .10$)⁽¹³⁾. It should be taken into account that the mean size of renal tumors in the study of Gill et al. was smaller than the present study (28 mm for LPN and 33 mm for OPN) and as such, patients in OPN group had significantly larger tumors ($P = .005$). But in the present study, the mean size of renal masses was not different in the two groups ($P = .30$). Another large retrospective study by Gill et al. on 1800 patients indicated that patients with decreased performance status, larger tumors and centrally located kidney tumors had undergone OPN rather than LPN. In these cases, LPN was accompanied with shorter surgical time, decreased operative blood loss and shorter hospital stay. However, LPN was associated with longer ischemia time and increased urologic complications. The chance of intraoperative complications and renal function, which changes after 3 months were similar in the two groups⁽¹⁴⁾. Similarly, a review article by Porpiglia et al. indicated longer WIT for LPN than OPN⁽¹⁵⁾. A study by Gong et al. on patients with stage T1a of renal tumors suggested longer operation and ischemic time for LPN than OPN. However, laparoscopy was associated with less blood loss, hospital stay and

post-operative complications⁽¹⁶⁾. The results from the Italian multicenter "RECORD" project also indicated a longer WIT for LPN than OPN. Nevertheless, GFR was not significantly different after 6 months⁽¹⁷⁾. On the other hand, a literature review on the role of minimally invasive techniques for kidney masses suggested shorter ischemia time, lower complication rate and decreased morbidity for LPN in contrast to OPN⁽¹⁸⁾. A multicenter retrospective study by Crepel and associates indicated longer surgical time for LPN than OPN. Intraoperative blood loss and complications were similar in the two groups. Laparoscopy was associated with shorter hospital stay, while LPN was done in smaller and more peripheral tumors. Therefore, this study suggested that "the indications for laparoscopic partial nephrectomy remain selective"⁽¹⁹⁾. Another retrospective study by Marszalek et al. demonstrated that WIT, hospital stay and surgical time were lower in LPN than OPN group. Surgical hemorrhage, adverse effects and GFR changes were comparable in the two groups⁽²⁰⁾. Similarly, Springer et al. concluded that WIT is lower in LPN than OPN; but there was no significant difference between long term GFR and oncologic outcomes⁽²¹⁾. As stated above, irrespective of whether WIT was longer or shorter in LPN than in OPN, the mean long term GFR was always comparable to open surgery as shown in several studies^(14,15,17,20,21). Moreover, this study presents similar results in stage T1a of renal tumors. However, it should be noted that the surgeon's expertise and tumor accessibility are two important factors that may influence ischemic time⁽¹⁷⁾. Most studies suggest that peri-operative complications are similar between LPN and OPN. Some studies indicated that surgical bleeding is lower during laparoscopy^(13, 16, 18). In the study, the mean hemorrhage and hemoglobin drop were not different in two groups. Open partial nephrectomy was associated with more cases of pleural injury, which was due to flank surgical approach. However, the rate of urologic complications and urinary leakage was significantly higher in the LPN group. This result is consistent with earlier retrospective studies^(8,13,14), and maybe due to difficulty in the repair of pyelocalyceal system and Dj insertion during laparoscopy. Earlier studies have warned about margin involvement in laparoscopic surgery, which may be attributed to lack of tactile sense during surgery^(13,22,23). Higher rates of margin positive cases in LPN than OPN were observed in this study, although not statistically significant, but suggests extra precision and wider margin excision for laparoscopy to warrant a margin-free pathology. More prospective studies with long-term follow up are needed to evaluate the oncologic outcomes of this difference. This study, as the first clinical trial in this field, is accompanied with several limitations. Patient randomization was not possible due to ethical issues and paucity of strong evidence about feasibility of LPN in all types of renal tumors. In addition, relatively small sample size and short follow up may affect the results of this study. More prospective multi-center surveys with long-term follow up and large volume population are necessary to justify the information obtained by this study.

CONCLUSIONS

LPN is an acceptable alternative to OPN in clinical stage T1a of renal tumors. It has some advantages over OPN such as more patient satisfaction

scores and better post-operative pain control. The mean hospital stay, WIT, intra-operative hemorrhage, peri-operative complications and changes in GFR are comparable to OPN. However, while LPN is selected as the primary choice, extra caution is required about tumor margin and urinary leakage.

ACKNOWLEDGEMENTS

This article has been extracted from the thesis written by Dr. Gholam Hossein Rezaeetalab in school of Medicine, Shahid Beheshti University of Medical Sciences. (Registration No: 278M).

CONFLICT OF INTEREST

No conflict of interest is declared.

REFERENCES

- Herr HW. A history of partial nephrectomy for renal tumors. *J Urol.* 2005;173:705-8.
- Ficarra V, Secco S, Fracalanza S, et al. Expanding indication for elective nephron-sparing surgery in renal cell carcinoma. *Arch Ital Urol Androl.* 2009;81:86-90.
- Van Poppel H, Becker F, Cadeddu JA, et al. Treatment of localised renal cell carcinoma. *Eur Urol.* 2011;60:662-72.
- Nguyen CT, Campbell SC, Novick AC. Choice of operation for clinically localized renal tumor. *Urol Clin North Am.* 2008;35:645-55; vii.
- Johnston WK, 3rd, Wolf JS, Jr. Laparoscopic partial nephrectomy: technique, oncologic efficacy, and safety. *Curr Urol Rep.* 2005;6:19-28.
- Berger A, Crouzet S, Canes D, Haber GP, Gill IS. Minimally invasive nephron-sparing surgery. *Curr Opin Urol.* 2008;18:462-6.
- Novick AC. Laparoscopic and partial nephrectomy. *Clin Cancer Res.* 2004;10:6322s-7s.
- Weise ES, Winfield HN. Laparoscopic partial nephrectomy. *J Endourol.* 2005;19:634-42.
- Hadjipavlou M, Khan F, Fowler S, Joyce A, Keeley FX, Sriprasad S. Partial vs radical nephrectomy for T1 renal tumours: an analysis from the British Association of Urological Surgeons Nephrectomy Audit. *BJU Int.* 2015.
- Berger AK, Stein RJ, Aron M, Gill IS, Desai MM. Laparoscopic partial nephrectomy: a decade of evolution. *J Endourol.* 2011;25:145-50.
- Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol.* 2015;67:913-24.
- Van Poppel H. Efficacy and safety of nephron-sparing surgery. *Int J Urol.* 2010;17:314-26.
- Gill IS, Matin SF, Desai MM, et al. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. *J Urol.* 2003;170:64-8.
- Gill IS, Kavoussi LR, Lane BR, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. *J Urol.* 2007;178:41-6.
- Porpiglia F, Volpe A, Billia M, Scarpa RM. Laparoscopic versus open partial nephrectomy: analysis of the current literature. *Eur Urol.* 2008;53:732-42; discussion 42-3.
- Gong EM, Orvieto MA, Zorn KC, Lucioni A, Steinberg GD, Shalhav AL. Comparison of laparoscopic and open partial nephrectomy in clinical T1a renal tumors. *J Endourol.* 2008;22:953-7.
- Minervini A, Siena G, Antonelli A, et al. Open versus laparoscopic partial nephrectomy for clinical T1a renal masses: a matched-pair comparison of 280 patients with TRIFECTA outcomes (RECORD Project). *World J Urol.* 2014;32:257-63.
- Heuer R, Gill IS, Guazzoni G, et al. A critical analysis of the actual role of minimally invasive surgery and active surveillance for kidney cancer. *Eur Urol.* 2010;57:223-32.
- Crepel M, Bernhard JC, Bellec L, et al. [Comparison of open and laparoscopic partial nephrectomy: a French multicentre experience]. *Prog Urol.* 2007;17:45-9.
- Marszalek M, Meixl H, Polajnar M, Rauchenwald M, Jeschke K, Madersbacher S. Laparoscopic and open partial nephrectomy: a matched-pair comparison of 200 patients. *Eur Urol.* 2009;55:1171-8.
- Springer C, Hoda MR, Fajkovic H, et al. Laparoscopic vs open partial nephrectomy for T1 renal tumours: evaluation of long-term oncological and functional outcomes in 340 patients. *BJU Int.* 2013;111:281-8.
- Lifshitz DA, Shikanov SA, Deklaj T, Katz MH, Zorn KC, Shalhav AL. Laparoscopic partial nephrectomy for tumors larger than 4 cm: a comparative study. *J Endourol.* 2010;24:49-55.
- Breda A, Stepanian SV, Liao J, et al. Positive margins in laparoscopic partial nephrectomy in 855 cases: a multi-institutional survey from the United States and Europe. *J Urol.* 2007;178:47-50; discussion