先進医療総括報告書の指摘事項に対する回答１

先進医療技術名：内視鏡下手術用ロボットを用いた腹腔鏡下腎部分切除術

2015 年 8 月 13 日

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今回の先進医療 B の対照となるヒストリカルデータとして提示された参考文献１（Saito H, et al. J Endourol 26:652-659, 2012）は、1998 年から 2008 年の全国の腹腔鏡下腎部分切除例のデータを示しているもので、かなり古いデータであるように感じる。最近 2―3 年の腹腔鏡下腎部分切除における阻血時間（上記文献の warm ischemic time に相当すると思われるが）は、当該論文の中央値 35 分（era 3　2007 年 1 月～2008 年 12 月）よりも更に短縮しているのではないか？

総括報告書の中で、最近の技術的進歩による阻血時間の短縮については参考論文３２（Williams SB, et al. World J Urol 31:793-798, 2013） を参照しているところと承知するが、我が国の直近 2―3 年の新しい現状を確認したいという主旨で、その他学会報告、論文報告等で、そのような最近の阻血時間の相場を示すものがあれば、ご教示されたい。

【回答】

直近の 3 年間に発表された、本先進医療のヒストリカルコントロールとほぼ同様の腹腔鏡下腎部分切除術を行った国内施設からの 5 報告を添付致しますのでご参照ください。

a) 学会報告：日本泌尿器内視鏡学会（2014）／2 件

① 大畠領ほか「当科における腹腔鏡下腎部分切除術の治療成績」（2012 年～2014 年）［日本泌尿器内視鏡学会（2014）抄録【O-084】］

22 例（T1a：18 例、T1b：1 例、多発腫瘍：1 例、腎血管筋脂肪腫：2 例）を対象に検討をしており、阻血時間：28 分 12 秒（平均値）、腫瘍径：28.6 ㎜（平均値）でした。

② 三田耕司ほか「V-Loc を用いた無結紮連続縫合腹腔鏡下腎部分切除術の治療成績」（2011 年～2014 年）［日本泌尿器内視鏡学会（2014）抄録【O-081】］

42 例を対象に検討しており、阻血時間：23 分（中央値）、摘出重量：22 ｇ（中央値）でした。

b） 論文報告／3 件

① 2009 年～2011 年に腹腔鏡下腎部分切除を施行した 41 例を対象とした報告
［N Masumori et al. New technique with combination of felt, Hem-o-lok and Lapra-Ty for suturing the renal parenchyma in laparoscopic partial nephrectomy. International Journal of Urology. 2012;19(3):273-6.］

阻血時間：28 分（中央値）（range 9–53）、腫瘍径：21 mm（中央値）（range 8–38）でした。

② 腹腔鏡下腎部分切除術を施行した 58 例の腎腫瘍患者を対象に腎動静脈クランプ、または腎動脈クランプを行った場合の術後への影響を比較した報告
［Y Funahashi et al. Comparison of Renal Ischemic Damage During Laparoscopic Partial Nephrectomy with Artery-Vein and Artery-Only Clamping. Journal of Endourology. 2014;28(3):306-11.］

腹腔鏡下腎部分切除術施行時期は、腎動静脈クランプ群（AV 群）26 例は 2005 年 8 月～2010 年 12 月、腎動脈クランプ群（AO 群）32 例は 2011 年 1 月～2013 年 1 月でした。各群の阻血時間および腫瘍径（平均値±標準偏差）は、AV 群が阻血時間：26.3±6.5 分（range 15-38）、腫瘍径：3.0±1.5 cm、AO 群が阻血時間：30.7±5.6 分(range 22–46)、腫瘍径：2.8±1.1 cm でした。

③ 2007 年～2012 年に腹腔鏡下腎部分切除術を受けた T1a（腫瘍径 4 cm 以下）の 63 例を対象とした報告
［K Osaka et al. Predictors of trifecta outcomes in laparoscopic partial nephrectomy for clinical T1a renal masses. International Journal of Urology. 2015.］

阻血時間 25 分未満は 42 例（66.7％）でした。全症例（63 例）中 4 例（6.3％）に切除断端陽性を認めています。阻血時間：21 分（中央値）、腫瘍径：24 mm（中央値）、腫瘍切除重量：10 g（中央値）でした。

本先進医療の有効性の解析対象集団（FAS）の 103 例（うち、3 例はプロトコル治療未実施）では、腫瘍径が 4 cm を超える T1b 症例が 9 例含まれ、腫瘍径の平均値は 26.7 ㎜、中央値は 25 ㎜、腫瘍切除重量の平均値は 21.40 g、中央値は 15 g でした。

Osaka らの報告［b）-③］を参照するにあたっては、本先進医療の腫瘍径の中央値が Osaka らの報告よりも大きく、かつ腫瘍切除重量の中央値が Osaka らの報告の 1.5 倍であった点を考慮することが適切と考えます。また、Osaka らの報告において本先進医療の主要評価項目を評価するにあたり、仮に阻血時間が 25 分以上の症例にすべての切除断端陽性症例が含まれるとした場合でも、阻血時間 25 分未満かつ切除断端陰性の率は最大で 66.7%と推察されます。

これに対し、本先進医療の FAS では、阻血時間 25 分以内：91.3%、切除断端陽性：0%、阻血時間：19 分（中央値）、19.0±6.4 分（平均値±標準偏差）、といずれの項目においても Osaka らの報告に比べ優っています。また、腫瘍径：25 ㎜(中央値)、腫瘍切除重量：15 g(中央値)から推察すれば Osaka の報告より大きな腫瘍を切除していると考えられます。

さらに、本先進医療の主要評価項目である周術期終了時点における腎機能温存かつ根治切除率（腹腔鏡下手術または開腹手術に非移行、切除断端陰性かつ腎阻血時間 25 分以内の割合）は 91.3%で、その 95%信頼区間の下限は 84.1%であり、Osaka らの報告から推察した値 66.7%に比べ高い値となっています。

以上、それぞれの報告を参照するにあたっては、腫瘍径、切除重量に差が見られ阻血時間が少なからず影響を受けること、参考文献 1（症例数 1375 例、era3 の症例数 604 例）に比べて症例数がかなり少ないことを考慮すべきと思いますが、最近の我が国の施設からの上記の報告を基にすれば腹腔鏡下腎部分切除術の阻血時間は、概ね 21 分から 30 分と推察されます。

O-081 V-Locを用いた無結紮連続縫合腹腔鏡下腎部分切除術の治療成績

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広島市立安佐市民病院　泌尿器科

【目的】腎腫瘍に対しV-Locを用いた無結紮連続縫合腹腔鏡下腎部分切除術(LPN)の治療成績を検証する。【方法と対象】2011年より2014年までに当院で施行したV-Locを用いた無結紮連続縫合腹腔鏡下腎部分切除術42例を対象とし臨床的な検討を行った。分腎機能変化はMAG3レノグラムを用いて算出した。【結果】全症例の年齢65.5歳、男:女=26例:16例、右:左=21例:21例、BMI24.1、腫瘍径24mm、RENAL nephrometry score(RNS)は、4:2例、5:7例、6:3例、7:9例、8:10例、9:10例、10:1例、アプローチは後腹膜21例:経腹膜21例、阻血時間23分、気腹時間189分、出血量15ml、摘出重量22g(中央値)で開腹術移行症例はなく、全例切除断端は陰性であった。観察期間中の術後1例に後出血がみられたが自然軽快した。術後の観察期間中に再発症例はみられず、術後の画像上の著変はみられなかった。術前後の腎機能の推移は術前eGFRを100%とした場合、術後1、3、12ヶ月目のeGFRはそれぞれ91.1%、97.6%、94.3%で推移したが、MAG3レノグラムによって算出した術後3ヶ月目の分腎機能は術前を100%とした場合、健側が109.8%、患側が74.7%にそれぞれ変化していた。【結論】比較的RNSの高い症例が含まれていたが今回の検証から腎腫瘍に対するV-Locを用いた無結紮連続縫合腹腔鏡下腎部分切除術(LPN)は有用と考えられた。

O-082 腹腔鏡下腎部分切除術におけるキドニークランプ®を用いた腎実質クランプ法の検討

岡本　雅之、岡村　泰義、石田　貴樹、奥野　優人、田口　功、川端　岳

関西労災病院　泌尿器科

【目的】腹腔鏡下腎部分切除術におけるキドニークランプ®(カールストルツ社)の有用性について検討を行った。【対象と方法】対象は当科にて腎実質クランプ法による腹腔鏡下腎部分切除術を施行した18例。年齢は21-85歳(中央値62歳)、腫瘍径は13-62mm(中央値28mm)、腫瘍の部位は上極8例、下極10例であった。後腹膜あるいは経腹膜アプローチで腫瘍に到達・同定し、切除予定ラインより約1～2cm外側の腎実質にキドニークランプ®をかけ阻血を行った。腫瘍切除面の止血、尿路開放部の縫合を行ったのちクランプを解除、必要に応じ実質縫合を追加した。【結果】手術時間は199-405分(中央値271分)、クランプ時間は11-70分(中央値25分)、出血量は10-300 g(平均値60g)で、開放手術や腎摘除術への移行、輸血を必要とした症例を認めなかった。術前、術直後、術後3～6カ月におけるeGFRの平均値は各々63,53,61(ml/min/1.73m2)であり、腎シンチグラフィによる患側腎機能の低下を示す% reductionの平均値は16%であった。【結論】本法は腫瘍の部位により適応は限定されるが、腎実質を直接クランプし、血流を制御することで、安全に手術を施行できた。腎機能保持の面に関しては腎門部クランプ法と同様の結果であった。

O-083 飯塚病院泌尿器科における腹腔鏡下腎部分切除術の検討

足立知大郎、中島　雄一

飯塚病院　泌尿器科

目的：飯塚病院泌尿器科で施行された腹腔鏡下腎部分切除術についての検討　対象：2000年1月～2013年12月までに飯塚病院泌尿器科で施行された腎癌に対する腹腔鏡下腎部分切除術について検討した。13例、13腎に対して手術されており、全てT1aであった。年齢の中央値は65才、男女比は9:1、患側は左:右が7:4、手術時間は320分(中央値)、出血量は387ml(中央値)、在院日数は14日(中央値)であった。切除方法はマイクロターゼ使用が8例、血流遮断が3例であった。

O-084 当科における腹腔鏡下腎部分切除術の治療成績

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当科では2年前より腹腔鏡下腎部分切除術を開始し，これまでに23例に手術を行った．対象は2012年4月より2014年6月までの腹腔鏡下腎部分切除術を行った23例のうち，術中迅速で断端陽性とされ腎摘術へ移行した1例を除く22例で，年齢は平均61歳，平均BMI23.7，右13例，左9例，経腹アプローチ10例，後腹膜アプローチ12例であった．両側腎癌でそれぞれ部分切除を行った症例は左右それぞれ1例とした．術前診断はAML2例，腎癌20例(cT1a：18例，cT1b：1例，多発腫瘍：1例)であった．腫瘍径は平均28.6mmでRENAL scoreは4－6点が9例，7－9点が13例であった．平均手術時間は251分(160～354分：尿管カテーテル挿入時間含む)，平均気腹時間192分(127～289分)，出血量126ml(5～805ml)，平均阻血時間は28分12秒(9～45分)であった．腎杯開放は13例に認め，術後1例に仮性動脈瘤が生じ塞栓術が必要となった．病理診断では2例がAML，1例がオンコサイトーマ，結果の判明した18例はすべて腎癌であった．術前の平均eGFRは89.5ml/min，術後1ヶ月の平均eGFRは80.3ml/minであった．永久標本での切除断端は全て陰性であった．小径腎腫瘍に対する腹腔鏡下腎部分切除術は，腎機能温存はもちろん，切開創も小さく低侵襲と考えられ積極的に行うべき手術方法と考えられる．

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Skills and Pitfalls

New technique with combination of felt, Hem-o-lok and Lapra-Ty for suturing the renal parenchyma in laparoscopic partial nephrectomy

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Abbreviations & Acronyms
PN = partial nephrectomy

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Abstract: We reported a new technique for closure of the renal parenchyma in laparoscopic partial nephrectomy, shortening the suturing time. Between 2009 and 2011, 41 patients with renal masses 4 cm or smaller in diameter underwent transabdominal laparoscopic partial nephrectomy by a single surgeon in a single institution. The sutures were carried out using 2-0 vicryl CT-1 with a 1.2 × 1.2 cm piece of felt, and both sutures were temporarily held using a Hem-o-lok. After all sutures (median 3) were completed, they were sequentially fixed by sliding the Hem-o-lok, and then locked using the Lapra-Ty. The median times for suturing the renal parenchyma and ischemic time were 13 min and 28 min, respectively. The arrangement of the wound and hemostasis were good. No patients developed urinoma or postoperative bleeding.

Key words: laparoscopy, new technique, parenchymal suture, partial nephrectomy.

Introduction

Although its minimal invasiveness is attractive, laparoscopic PN is still a challenging procedure.[1] When the renal vessels are clamped, it is mandatory to shorten the ischemic time as much as possible to avoid renal damage. The time-controlling step of the ischemic time is the suturing procedure for the renal parenchyma. Although several procedures have been proposed, including interrupted sutures,[2] running sutures using a long thread[3–5] and using clips to substitute for knot tying,[6,7] to suture the parenchyma speedily and securely is sometimes difficult. For the wide use of laparoscopic PN as a standard surgical procedure, it is mandatory to develop a technique that can be carried out speedily and safely. In the present study, we report a new technique for closure of the renal parenchyma.

Surgical technique

Between May 2009 and August 2011, 41 patients with small renal masses 4 cm or smaller in diameter underwent transabdominal laparoscopic PN using a new suturing technique by a single surgeon (NM) in Sapporo Medical University.

Regardless of the location of the tumor, the transperitoneal anterior approach was used. All renal arteries were clamped with bulldog forceps, then irrigation of cold saline through the ureteral catheter was started to cool down the renal parenchyma.[8] After tumor resection was carried out using a cold knife, the resection plane was coagulated with bipolar forceps. If the collecting system was opened, it was closed using 3-0 Vicryl. Then, the parenchymal suturing was carried out at intervals of 1 cm (Fig. 1). The details of the new procedure are described in the legend of Figure 2 (also see Video Clip S1). No patients received interposition using a bolster or vascularized perirenal adipose tissue. After declamping, threads with needles were cut out and taken from the abdominal cavity, then fibrin glue (Bolheal; Astellas Pharma, Tokyo, Japan) was applied.

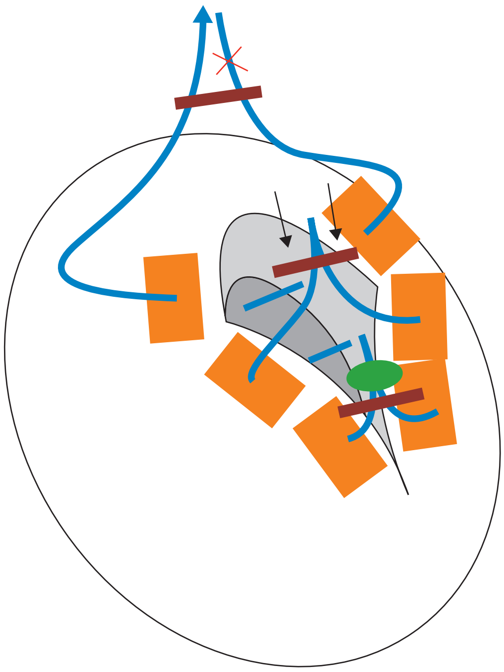

Fig. 1 New technique for suturing the renal parenchyma with a combination of felt, Hem-o-lok and Lapra-Ty. ▬, Hem-o-lok; ―, 2-0 Vicryl CT-1; ×, knots; ●, Lapra-Ty; ◆, felt.

Table 1 Characteristics and surgical outcome of 41 patients who underwent laparoscopic partial nephrectomy

Median age, years (range)	58 (36–81)
Male/female	25/16
Median body mass index, kg/m² (range)	24.4 (16.9–36.1)
Indication, imperative/elective	2/39
Tumor laterality, right/left	24/17
Tumor location, upper pole/middle/ lower pole/renal hilum	9/14/13/5
Tumor flasking, exophytic/central*	27/14
Median tumor size, cm (range)	2.1 (0.8–3.8)
Renal vascular clamp, artery only/artery + vein	10/31
Median time for tumor resection, min (range)	5 (2–12)
No. patients with closure of the collecting system (%)	20 (48.8%)
Median time for parenchymal suturing, min (range)	13 (5–28)
Two sutures (*n* = 4)	9 (5–11)
Three sutures (*n* = 25)	12 (9–22)
Four sutures (*n* = 10)	18 (13–28)
Five sutures (*n* = 2)	22 (20, 24)
Median ischemic time, min (range)	28 (9–53)
Without closure of the collecting system (*n* = 21)	25 (9–47)
With closure of the collecting system (*n* = 20)	32.5 (25–53)
Median operation time, min (range)	187 (127–285)
Median estimated blood loss	100 (15–1300)
Blood transfusion (%)	0 (0)
Conversion to an open procedure (%)	0 (0)
No. patients with cheese wiring (%)	1 (2.4)
Urinoma (%)	0 (0)
Postoperative bleeding	0 (0)
Histology, renal cell carcinoma/benign tumor	38/3
Positive surgical margin (%)	0 (0)

*Central, tumors completely buried in the renal parenchyma.

Results

The characteristics of 41 patients are shown in Table 1. The median time for suturing the renal parenchyma was 13 min, ranging from 5 to 28 min (Table 1; Fig. 3). The median time for suturing was longer, as the number of sutures increased. For two patients with continuous slight bleeding from the wound even after application of the fibrin glue, a tissue-sealing sheet (TachoComb; CSL Behring, Tokyo, Japan) was applied.

Comments

By using the combination of the felt, Hem-o-lok and Lapra-Ty, we could achieve short ischemic time through a short time for suturing. This new technique assured the safety of the suturing with firm alignment of the wound and avoidance of the cheese wiring (incision of the renal parenchyma by the thread). Because the sutures were carried out roughly and temporarily held by the Hem-o-lok, we could clearly see the bottom of the wound for suturing. In addition, the felt was helpful to avoid the cheese wiring when the threads were sequentially fixed by sliding the Hem-o-lok and locked with the Lapra-Ty.

There are several technical tips to apply to the new technique. First, to fix the threads by sliding the Hem-o-lok using the needle holder, it is important to make an isosceles triangle shape between the threads to convey equal force on both sides of the wound. Second, the felt should be appropriately placed on the surface of the renal parenchyma to avoid cheese wiring. Third, if each thread is separately fixed by the Hem-o-lok, the Lapra-Ty should be applied on one thread, then the other thread is tightened again by sliding the Hem-o-lok, and finally a second Lapra-Ty is applied on the other thread (see Video Clip S2).

Conflict of interest

None declared.

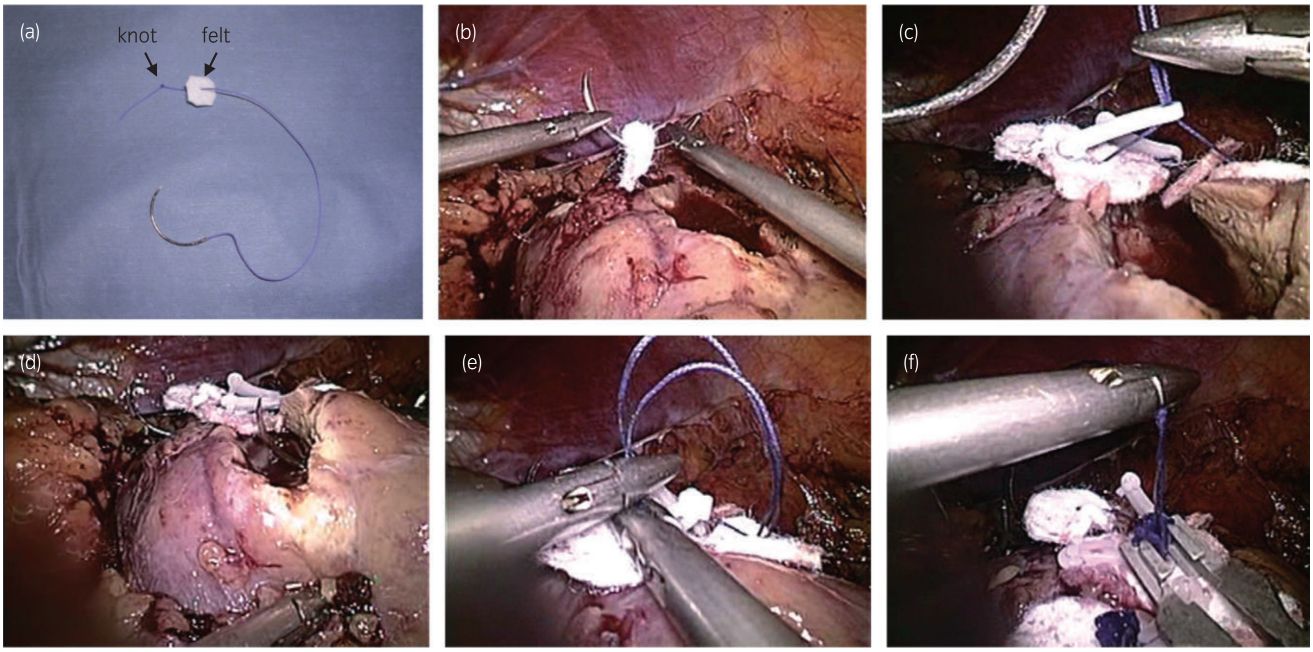

Fig. 2 Steps of the interrupted suture with ligation using felt, a Hem-o-lok and Lapra-Ty. (a) Double knots are made 2 cm from the terminal end of 18 cm of 2-0 Vicryl with a CT-1 needle. A 1.2 × 1.2 cm piece of felt is attached on the proximal side of the knots. (b) Once each suture is done, the felt is applied through the needle. The suturing is started from the back of the wound. (c) Both threads are temporarily held using an L-size Hem-o-lok. It is crucial to make an isosceles triangle-shape between the threads. (d) All sutures can be carried out under a clear view of the bottom of the wound, because the threads are not fully tightened yet. (e) The threads are fixed by sliding the Hem-o-lok using the needle holder. Care should be taken not to flip or dislocate the felt. (f) Then both threads are locked using the Lapra-Ty. Fixing and locking are sequentially carried out from the front to the back of the wound. Before cutting out the needles, the vascular clamps are removed and hemostasis is observed. Bleeding from the wound after declamping can usually be controlled by compression with gauze and the application of fibrin glue. It should be kept in mind that many sutures are required for a long wound, because the sutures are carried out at intervals of 1 cm. Thus, as the wound becomes longer, more time for suturing is necessary.

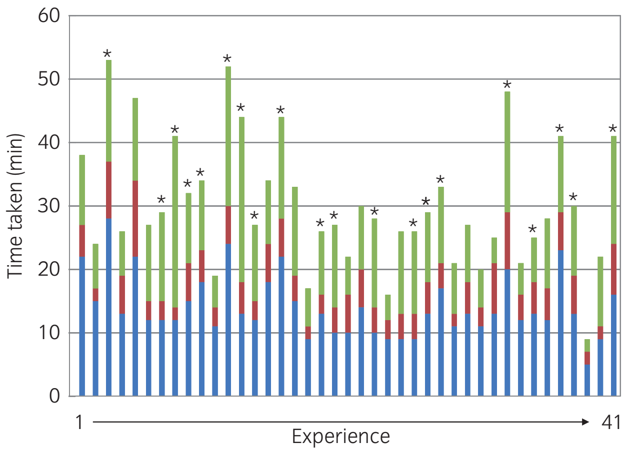

Fig. 3 Times for tumor resection and parenchymal suturing according to experience. *Patient with closure of the collecting system. ■, Time for tumor resection; ■, other time (coagulation, closure of the collecting system, etc.); ■, time for parenchymal suture.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Video Clip S1 Steps of the interrupted suture with ligation using felt, a Hem-o-lok and Lapra-Ty.
Video Clip S2 Technical tip to apply Lapra-Ty if each thread is separately fixed by a Hem-o-lok.

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Comparison of Renal Ischemic Damage During Laparoscopic Partial Nephrectomy with Artery-Vein and Artery-Only Clamping

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Abstract

Objective: To compare renal ischemic damage caused by artery-only (AO) and artery-vein (AV) clamping after laparoscopic partial nephrectomy.

Materials and Methods: We included 58 patients who underwent laparoscopic partial nephrectomy for nonhilar exophytic renal tumors in this study. AV clamping was used for 26 of these patients, while AO clamping was used for 32. All patients had a functional contralateral kidney. We assessed effective renal plasma flow (ERPF) by ^{99m}Technetium-mercaptoacetyltriglycine (^{99m}Tc-MAG3) renal scintigraphy preoperatively and at 1 week and 6 months postoperatively. In addition, we analyzed ^{99m}Tc-MAG3 uptake regionally in the surgically nonaffected areas.

Results: Mean tumor diameters were 3.0 cm in the AV group and 2.8 cm in the AO group. Warm ischemic time was significantly shorter in the AV group than the AO group (26.3 vs. 30.7 minutes, respectively, $p=0.007$). There were no differences in the estimated glomerular filtration rates or ERPF of the operated kidney between groups preoperatively or 1 week or 6 months postoperatively. The decrease in regional ^{99m}Tc-MAG3 uptake of the operated kidney at 1 week was correlated with warm ischemic time in both groups, being stronger in the AV group ($p<0.001$) than in the AO group ($p=0.027$). This decrease was significantly less in the AO group when the ischemic time was ≥ 25 minutes (88.1% vs. 102.5%, $p=0.001$).

Conclusions: Ischemic renal damage during laparoscopic partial nephrectomy was lessened by applying AO clamping particularly in cases with prolonged ischemic time.

Introduction

Partial nephrectomy achieves equivalent oncological outcomes, better postoperative kidney function, and better overall survival compared with radical nephrectomy; therefore, it is recommended for treating localized small renal tumors.[1–4] Laparoscopic or robotic-assisted partial nephrectomy is attractive due to its minimal invasiveness, which improves not only postoperative renal function, but also postoperative recovery and pain sensation.[5] However, there is a concern of renal ischemic injury to the preserved renal parenchyma because renal ischemia is usually conducted without kidney cooling during endoscopic partial nephrectomy.[6,7]

Artery-only (AO) clamping, with venous blood flow unclamped, has been proposed to minimize ischemic renal damage compared with artery-vein (AV) clamping,[8–10] and several studies have investigated the superiority of AO clamping to AV clamping, particularly in the face of the growing population of patients with older age, low baseline renal function, hypertension, or diabetes. However, because backflow blood from the renal vein is minimal during endoscopic surgery due to compression by the pneumoperitoneum pressure, the benefit of AO clamping during endoscopic partial nephrectomy is still controversial.[9,11,12] Most published partial nephrectomy series based their renal function assessments on the serum creatinine level or estimated glomerular filtration rate (eGFR).[5] However, these parameters are inappropriate for evaluating renal functional damage to an operated kidney in patients with bilateral kidneys because compensation by the functioning contralateral kidney masks the damage.[12–14] Therefore, quantification of split renal function is preferable for the precise evaluation of renal functional changes. In addition, renal function after partial nephrectomy is influenced by the amount of resected nephron and ischemic injury in the preserved renal tissue, and conventional methods cannot evaluate these factors. We

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previously reported regional ^{99m}Technetium-mercaptoacetyltriglycine (^{99m}Tc-MAG3) uptake as a new renal scintigraphy parameter,[14] which enables assessment only of the ischemic damage to the surgically preserved renal tissue after partial nephrectomy without being affected by tumor or patient characteristics.

In the present study, we compared postoperative renal function after laparoscopic partial nephrectomy with AV and AO clamping by using ^{99m}Tc-MAG3 renal scintigraphy parameters of effective renal plasma flow (ERPF) and regional ^{99m}Tc-MAG3 uptake to evaluate the benefit of AO clamping on postoperative renal function.

Materials and Methods

This study protocol was approved by the institutional review board at the Nagoya University Graduate School of Medicine before initiation. All patients provided written informed consent to enroll in the study.

Subjects

From August 2005 to January 2013, we performed laparoscopic partial nephrectomy with hilar clamping and no cooling on 75 patients. In our institute, we performed laparoscopic partial nephrectomy applying AV clamping before December 2010 and AO clamping for all cases since January 2011. Because the purpose of the present study was to assess the influence of clamping methods on postoperative changes in renal function without considering the complexities of tumor morphology, we excluded 1 endophytic tumor and 2 hilar tumors in the AV clamping group and 11 endophytic tumors and 3 hilar tumors in the AO clamping group. Tumors were defined as exophytic when the lesion extended >50% off of the natural surface of the kidney. After exclusion, we enrolled a total of 58 patients who underwent laparoscopic partial nephrectomy for nonhilar exophytic renal tumors; AV clamping was used in 26 of these patients and AO clamping was used in 32. All patients had a functional contralateral kidney. Patients who undergo partial nephrectomy at our institute ordinarily start to take a diet on postoperative day 1 and start to walk on postoperative day 2.

Surgical procedures

Key surgical procedures were performed similarly between the AV and AO clamping groups. We performed a laparoscopic partial nephrectomy through the abdominal cavity with 8–10 mmHg of pneumoperitoneal pressure. The renal artery and vein were clamped in an en bloc fashion with a Satinsky clamp before resecting the tumor for the AV clamping method, whereas the renal artery was separated and clamped with a laparoscopic bulldog clamp for the AO clamping method. Tumor margins were then excised by cold cutting, starting ~5 mm from the tumor edge. We routinely inserted a pigtail ureteral catheter into the renal pelvis just after anesthesia and carefully inspected the open renal collecting system by infusing indigo carmine after resecting the tumor. Clamping of renal blood flow was released after closure of the renal defect with knot-tying sutures, if necessary, over Surgicel® bolsters. Six surgeons performed the surgeries included in this study. Among them, two surgeons performed the operations in the AV group, and six surgeons performed the operations in the AO group. We checked for urinary leakage using an iodinated contrast agent on postoperative days 2–4 and removed the catheter when no urinary leakage was detected.

Serum creatinine and eGFR calculation

Serum creatinine was determined preoperatively and 1 week and 6 months postoperatively. eGFR was calculated using the current equation established for the Japanese population [eGFR (mL/minute/1.73 m^2) $= 194 \times Cr^{-1.094} \times age^{-0.287}$ ($\times 0.739$ for females)].[15]

Imaging procedures

All patients underwent ^{99m}Tc-MAG3 scintigraphy preoperatively and 1 week postoperatively. Patients who were followed for longer than 6 months in our hospital also underwent ^{99m}Tc-MAG3 scintigraphy at 6 months postoperatively (24 patients in the AV group and 28 in the AO group).

Patients were injected with ~200 MBq of ^{99m}Tc-MAG3. The injected dose was accurately measured by counting the radioactivity of the syringe before and after the injection. Posterior images were obtained for 30 minutes immediately after administration using a SKY Light gamma camera (Hitachi/Philips Co., Tokyo, Japan) with a low-energy general-purpose collimator. The regions of interest (ROIs) were drawn semiautomatically on the images of both kidneys using analyzing software, and ERPF corrected by the body surface area (1.73 m^2) was calculated using a camera-based technique.[16] Values obtained with this technique were compared by means of the single-sample ^{99m}Tc-MAG3 clearances calculated using the Bubeck equation.[17] ERPF was calculated using the following regression equation: ERPF (mL/minute/1.73 m^2) $= 9.825X + 11.258$, where X is the ^{99m}Tc-MAG3 renal uptake rate 1–2 minutes after injection.

We also assessed ^{99m}Tc-MAG3 uptake regionally in surgically nonaffected areas of the ipsilateral kidney as described previously[14] to determine the extent of ischemic damage. Briefly, kidney length was measured using a preoperative image, and ^{99m}Tc-MAG3 uptake was measured in one-fourth of the area on the opposite pole of the tumor (Fig. 1). We defined "regional ^{99m}Tc-MAG3 uptake" as the quotient of the uptake by area. An equivalent ROI was drawn on the postoperative image. For example, when the tumor was located at the lower pole and the kidney length was 40 pixels, the ROI was set in 10 pixels at the upper pole. All ROIs were drawn by a single radiologist who was blinded to the patients' clinical information.

Statistics

All values are expressed as mean ± standard deviation. Student's *t*-tests were used to compare parametric values. Correlation differences were calculated by Pearson's correlation coefficient. The chi-square test was used to compare ratios between the groups. Multiple regression analysis was used to determine the factors influencing the decrease in renal function. All tests were two sided, and *p*-values of <0.05 were considered to indicate statistical significance. Statistical analyses were performed with SPSS for Windows 16.0 (SPSS, Chicago, IL).

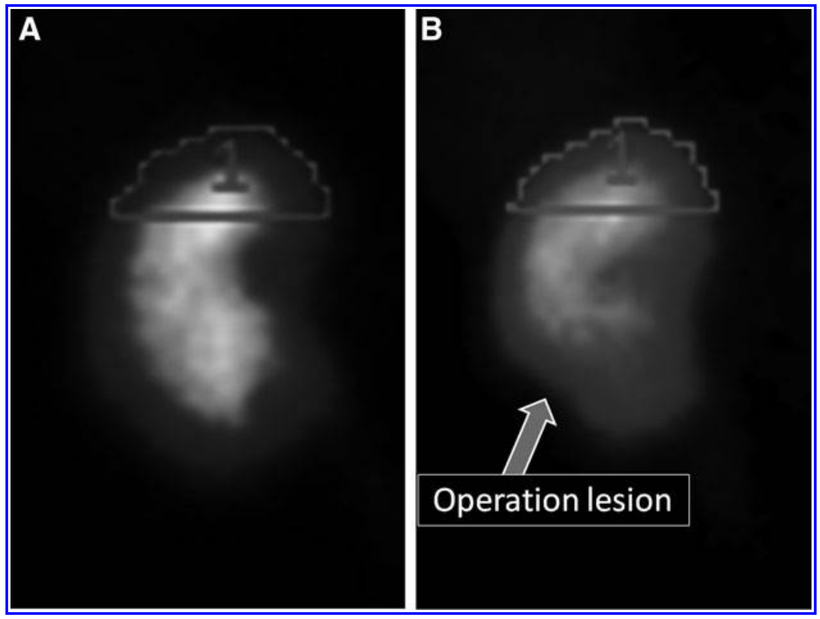

FIG. 1. Regional ^{99m}Technetium-mercaptoacetyltriglycine (^{99m}Tc-MAG3) uptake. The ^{99m}Tc-MAG3 uptake in the region of interest (ROI) set in a surgically non-affected part was divided by area. Compared with the preoperative image **(A)**, the ROI was set semiautomatically in the same area in the postoperative image **(B)**.

Results

Renal lesions were successfully excised from all patients. More endophytic and hilar tumor cases are performed with AO clamping at our institute. By excluding these tumors, the nephrometry score became almost equal between the AV and AO clamping groups (Table 1). There were no significant differences between the AV and AO groups in mean tumor size (3.0 vs. 2.8 cm, respectively; $p=0.424$) or R.E.N.A.L. (radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior, location relative to polar lines) nephrometry score (5.6 vs. 5.5 cm, respectively; $p=0.824$). Mean ischemia durations were significantly shorter in the AV group than in the AO group (26.3 minutes [range, 15–38 minutes] vs. 30.7 minutes [range, 22–46 minutes], respectively; $p=0.007$). Mean blood loss volumes were 144 and 172 mL, respectively ($p=0.810$), and one patient in the AV group and two patients in the AO group required a blood transfusion. Even though there was no significant difference in the estimated blood loss or transfusion rate between the two procedures, we recognized a disturbed tumor incision line during AO clamping due to oozing from the parenchyma. Postoperative urine leakage or hemorrhage was not noted in any patient. Postoperative histopathology revealed renal cell carcinoma in 48 patients, angiomyolipoma in 5, oncocytoma in 3, and hemorrhagic cysts in 2.

Mean serum creatinine levels in the AV group were 0.79, 0.87, and 0.86 mg/dL preoperatively, and 1 week and 6 months postoperatively, respectively (Table 2). The corresponding values in the AO group were 0.80, 0.87, and 0.83 mg/dL. eGFR values in the AV group were 74.7, 69.4, and 70.0 mL/minute/1.73 m^2 preoperatively, and 1 week and 6 months postoperatively, respectively; the corresponding values in the AO group were 68.7, 63.9, and 66.6 mL/minute/1.73 m^2. There were no statistically significant differences between the two groups at any time points. The number of patients with a 10% decline in eGFR at 1 week was 9 and 11 in the AV and AO groups, respectively ($p=0.985$).

ERPF in the operated kidney decreased by 15.2% (from 155.5 to 129.8 mL/minute/1.73 m^2, $p=0.001$) 1 week after surgery in the AV group, whereas that in the contralateral side increased by 9.8% (from 157.1 to 172.5 mL/minute/1.73 m^2, $p=0.004$) to compensate for this decrease. ERPF in the AO group decreased by 12.9% (from 151.8 to 129.9 mL/minute/1.73 m^2, $p<0.001$) on the operated side and increased by 7.0% (from 158.1 to 169.1 mL/minute/1.73 m^2, $p=0.005$) on the

Table 1. Patient Characteristics

	AV clamping	*AO clamping*	p-*Value*
No. of patients	26	32	
Patient age at surgery mean ± SD (range)	60.1 ± 15.1 (29–79)	63.6 ± 9.2 (41–82)	0.282
Gender (male/female)	21/5	22/10	0.299
Hypertension (y/n)	8/18	14/18	0.311
Diabetes mellitus (y/n)	4/22	3/29	0.485
Tumor size (cm) mean ± SD (range)	3.0 ± 1.5 (1.5–8.0)	2.8 ± 1.1 (1.3–6.0)	0.424
R.E.N.A.L. nephrometry score mean ± SD	5.6 ± 1.1	5.5 ± 1.3	0.824
Ischemic time (minute) mean ± SD (range)	26.3 ± 6.5 (15–38)	30.7 ± 5.6 (22–46)	0.007
Blood loss (mL) mean ± SD	144 ± 492	172 ± 413	0.810
Pathological findings (malignancy/benign)	22/4	26/6	0.736

AV = artery-vein; AO = artery-only; SD = standard deviation; R.E.N.A.L. = radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior, location relative to polar lines.

Table 2. Renal Functional Outcomes

	AV clamping	*AO clamping*	p-*Value*
Preoperation			
Serum creatinine (mg/dL)	0.79 ± 0.20	0.80 ± 0.18	0.816
eGFR (mL/minute/1.73 m^2)	74.7 ± 13.9	68.7 ± 10.9	0.072
ERPF (mL/minute/1.73 m^2)			
Normal side	157.1 ± 31.8	158.1 ± 33.6	0.906
Operated side	155.5 ± 32.5	151.8 ± 27.5	0.639
1 week postoperation			
Serum creatinine (mg/dL)	0.87 ± 0.26[a]	0.87 ± 0.22[a]	0.975
eGFR (mL/minute/1.73 m^2)	69.4 ± 16.3[a]	63.9 ± 11.3[a]	0.132
ERPF (mL/minute/1.73 m^2)			
Normal side	172.5 ± 31.9[a]	169.1 ± 32.5[a]	0.687
Operated side	129.8 ± 40.0[a]	129.9 ± 27.4[a]	0.991
6 months postoperation			
Serum creatinine (mg/dL)	0.86 ± 0.24[a]	0.83 ± 0.20	0.639
eGFR (mL/minute/1.73 m^2)	70.0 ± 16.7[b]	66.6 ± 11.8	0.398
ERPF (mL/minute/1.73 m^2)			
Normal side	173.2 ± 34.0[a]	159.1 ± 41.9	0.196
Operated side	126.8 ± 36.0[a]	124.4 ± 33.0[a]	0.806

All values are expressed as mean ± standard deviation. Paired *t*-test was done for 1 week and 6 months postoperative values to compare with preoperative ones.

[a]*p*-Value less than 0.01.

[b]*p*-Value less than 0.05.

eGFR = estimated glomerular filtration rate; ERPF = effective renal plasma flow.

nonoperated side. Thus, there were no significant differences in split renal function between the groups.

The relationships between ischemia time and regional ^{99m}Tc-MAG3 uptake at 1 week compared with the preoperative values are shown in Figure 2. In both groups, when ischemic time was short, regional ^{99m}Tc-MAG3 uptake decreased slightly or even increased to compensate for the decrease in renal function caused by nephron volume loss. The decreases in regional ^{99m}Tc-MAG3 uptake were larger with prolonged ischemic time. The difference between the groups increased with ischemic time. Pearson's correlation analysis showed a strong correlation between ischemic time and percent decrease in regional ^{99m}Tc-MAG3 uptake in the AV group ($p < 0.001$, $R^2 = 0.443$) and a weak correlation in the AO group ($p = 0.027$, $R^2 = 0.154$). The difference between the groups in regional ^{99m}Tc-MAG3 uptake values was small in all patients (98.6% vs. 104.0%, respectively, $p = 0.199$). However, when limited to cases with a warm ischemic time of ≥25 minutes, they were 88.1% in the AV group ($n = 14$) and 102.5% in the AO group ($n = 28$) ($p = 0.001$).

In multiple regression analyses, ischemic time ($\beta = -0.576$, $p = 0.002$) and hypertension ($\beta = -0.344$, $p = 0.048$) were significantly correlated with decrease in regional ^{99m}Tc-MAG3 uptake at 1 week in the AV group. Meanwhile, ischemic time ($\beta = -0.392$, $p = 0.027$) was the only independent predictor of a decrease in regional ^{99m}Tc-MAG3 uptake in the AO group (Table 3).

Discussion

Impaired renal function after partial nephrectomy is thought to occur as a result of ischemic damage to surgically preserved tissue and mass reduction of normal parenchyma resected with tumors. The present study evaluated changes in regional ^{99m}Tc-MAG3 uptake in addition to ERPF. The latter represents differential renal function [16–18]; however, the extent

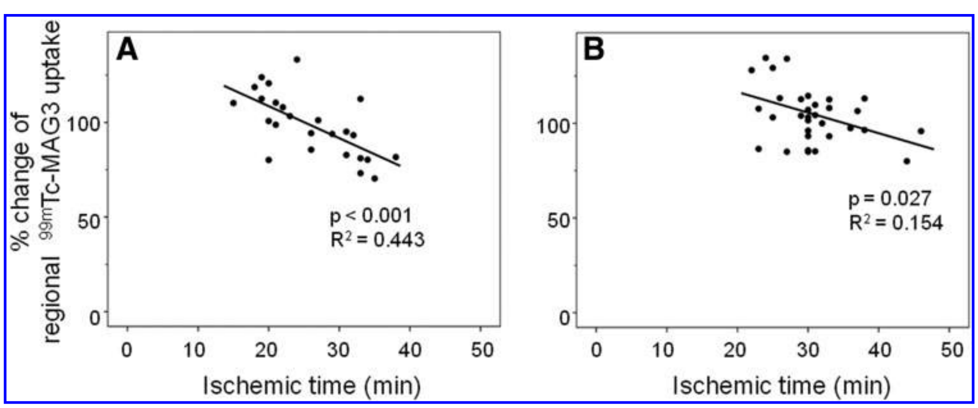

FIG. 2. Correlation between ischemic time and change in regional ^{99m}Technetium-mercaptoacetyltriglycine-(^{99m}Tc-MAG3) uptake. There was a strong correlation in the artery-vein group **(A)** and a weak correlation in the artery-only clamping group **(B)** between ischemic time and regional ^{99m}Tc-MAG3 uptake at 1 week as a percent of preoperative value. The difference between the two groups became apparent in cases with prolonged ischemic time.

Table 3. Multiple Regression Analyses for Percent Change in Regional ^{99m}Tc-MAG3 Uptake at 1 Week

	AV clamping		*AO clamping*	
	β	p-*Value*	β	p-*Value*
Age	−0.045	0.778	−0.037	0.832
Tumor size	0.015	0.940	0.248	0.209
R.E.N.A.L. nephrometry score	0.177	0.308	0.092	0.610
Ischemic time	−0.576	0.002	−0.392	0.027
Hypertension (y/n)	−0.344	0.048	−0.187	0.279
Diabetes mellitus (y/n)	−0.005	0.977	0.047	0.790

^{99m}Tc-MAG3 = ^{99m}Technetium-mercaptoacetyltriglycine; R.E.N.A.L. = radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior, location relative to polar lines.

of pure ischemic injury could not be evaluated. Consequently, we considered regional ^{99m}Tc-MAG3 uptake, which we reported previously to be correlated with warm ischemic time during open partial nephrectomy with AV clamping.[14] The results of the present study demonstrated that the change in postoperative regional ^{99m}Tc-MAG3 uptake was similar between the two groups when ischemic time was short, whereas it was smaller after AO clamping in cases with a prolonged ischemia duration.

Some studies have compared renal functional outcomes of AV clamping and AO clamping after laparoscopic partial nephrectomy. Imbeault et al. reported that the eGFR decrease was significantly smaller in the AV group and that the differential functional renal loss did not differ, although the warm ischemic time was significantly longer in the AO group. They concluded that AO clamping has no benefit.[8] In our study, ischemic time was also longer in the AO group, probably due to disturbed visualization of the tumor bed by venous oozing. This would be a shortage of the AO clamping. Gong et al. reported an advantage of AO clamping by showing no significant postoperative changes in creatinine or creatinine clearance after AO clamping in contrast to significant changes after AV clamping.[9] Orvieto et al. used a solitary kidney porcine model and investigated renal functional changes after AV clamping and AO clamping during open and laparoscopic surgery.[11] They found that AO clamping better protected the kidney compared with AV clamping during open surgery, but not during laparoscopic surgery. They speculated that the pneumoperitoneum caused at least partial occlusion of the renal vein during laparoscopic surgery, thus negating the benefit of AO clamping. The results of this study demonstrate that the benefit of AO clamping during laparoscopic partial nephrectomy is limited; however, it does facilitate preservation of renal function despite possible prolongation of ischemic time. Our group performs laparoscopic partial nephrectomy under 8–10 mmHg pneumoperitoneum pressure, which is lower than many other centers, where 12–15 mmHg is used. We are concerned that a pressure higher than venous pressure might disturb blood backflow from the renal vein. Maintaining a low pneumoperitoneal pressure may have led to subtle, but better preservation of renal function in our series.

We occasionally perform open partial nephrectomy without ischemia in cases of small exophytic tumors. However, we have always applied hilar clamping during laparoscopic partial nephrectomy. Some authors have reported their experience of laparoscopic partial nephrectomy for large or endophytic tumors with/without renal ischemia.[19,20] We plan to begin performing unclamped laparoscopic partial nephrectomy in selected cases as our experience increases.

Some limitations of this study should be mentioned. The number of patients was small in both groups, and the experience of surgeons in the two groups was not identical, which may have influenced ischemic duration or postoperative renal function. Despite these weaknesses, the results of our study demonstrate that AO clamping prolonged the upper limit of warm ischemia during laparoscopic partial nephrectomy to minimize deteriorating renal function.

Conclusions

We evaluated postoperative renal function after laparoscopic partial nephrectomy using renal scintigraphy and compared ischemic damage secondary to AV and AO clamping. Ischemic renal injury during laparoscopic partial nephrectomy was smaller when applying AO clamping compared with AV clamping when the ischemic time was prolonged to ≥25 minutes. Applying AO clamping is beneficial for preserving renal function despite the fact that it might prolong the ischemic time during laparoscopic partial nephrectomy.

Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

^{99m}Tc-MAG3 = ^{99m}Technetium-mercaptoacetyltriglycine
AO = artery-only
AV = artery-vein
eGFR = estimated glomerular filtration rate
ERPF = effective renal plasma flow
ROI = region of interest

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Original Article

Predictors of trifecta outcomes in laparoscopic partial nephrectomy for clinical T1a renal masses

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Abbreviations & Acronyms
ASA = American Society of Anesthesiologists
BMI = body mass index
CKD = chronic kidney dysfunction
eGFR = estimated glomerular filtration rate
LPN = laparoscopic partial nephrectomy
NSS = nephron-sparing surgery
OPN = open partial nephrectomy
PN = partial nephrectomy
PSM = positive surgical margins
TIT = total ischemia time
UCS = urinary collecting system

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Objectives: To assess trifecta outcomes for laparoscopic partial nephrectomy for clinical T1a renal masses.
Methods: A total of 63 patients who underwent laparoscopic partial nephrectomy for clinical T1a renal masses by a single surgeon between January 2007 and December 2012 were evaluated. Demographic and perioperative data were collected and statistically analyzed. We retrospectively evaluated trifecta outcomes. Multivariable logistic regression models were used to analyze predictors of trifecta outcomes. Trifecta outcomes were defined as the combination of total ischemia time <25 min, negative surgical margins and no surgical complications.
Results: Of the 63 patients, 39 (62%) achieved trifecta. A total of 21 patients had total ischemia time ≥25 min, four patients had positive surgical margins and two patients had surgical complications. Tumor size ($P < 0.001$), distance from the urine collecting system or sinus ($P < 0.001$) and surgeon's learning curve ($P < 0.01$) were significantly different between the trifecta and no-trifecta group. Multivariate analysis showed tumor size and surgeon's learning curve to be independent predictors of trifecta outcomes.
Conclusions: Tumor size and surgeon's learning curve seems to be strong predictors of trifecta outcomes after laparoscopic partial nephrectomy in T1a renal masses.

Key words: laparoscopy, partial nephrectomy, single surgeon, T1a renal masses, trifecta.

Introduction

Small renal masses are diagnosed more frequently because of the improvement and widespread use of abdominal imaging techniques.[1] With the increasing detection of small renal masses, there has been a dramatic increase in the opportunities to treat renal masses by minimally invasive interventions, such as NSS and probe ablative therapies. Despite recent developments in probe ablative therapies, PN is the standard therapy for small renal masses, with oncological equivalence, functional superiority and improved overall survival compared with radical nephrectomy.[2] Although LPN requires advanced laparoscopic skills and a steep learning curve, its surgical results when carried out by experienced surgeons are comparable with those of OPN.[3] Clinical T1a renal masses are considered as a good indication for LPN, because tumors with a high RENAL score tended to be managed with OPN or RAPN.

Since the trifecta concept, defined as a combination of negative surgical margins, minimal renal function decrease and no perioperative complications, was introduced to evaluate PN success, several NSS techniques have been evaluated as equivalent, regardless of the surgical approach.[4–8]

No reports on pure LPN trifecta outcomes for clinical T1a renal masses by a single surgeon have been published. Therefore, we evaluated the accomplishment of trifecta outcomes (defined TIT <25 min, negative surgical margins and no surgical complications) by assessing patient characteristics, tumor factors, operative data and surgeon's learning curve.

Methods

A total of 89 patients with primary renal tumor who underwent LPN between April 2008 and December 2012, and were followed up for longer than 1 year at Yokohama City University Hospital (Yokohama, Kanagawa, Japan) were included in the present study.

Surgical indications for PN were generally defined as cases with a tumor size ≤4.0 cm in our institution. In highly complex cases, OPN was sometimes chosen as per the surgeon's preference, and LPN was used in the other cases. LPN was also used if desired by the patient.

Of the 89 patients, 26 patients with solitary kidney, bilateral disease, multiple tumors or incomplete data were excluded. We thus analyzed the clinical data of 63 consecutive patients with a single localized unilateral renal tumor of size ≤4.0 cm and a normal contralateral kidney. All LPN procedures were carried out by a single laparoscopic surgeon (KM).

The study's main measured outcome was trifecta accomplishment. Furthermore, we examined the predictive factors, including patients' clinical, demographic and tumor factors, as well as surgeon's learning curve, for trifecta accomplishment. We defined trifecta outcomes as a combination of TIT <25 min, negative surgical margins and no surgical complications.[4–11] Patient preoperative demographic and tumor characteristics, including age, sex, BMI, ASA status, serum creatinine, rate eGFR, tumor location and size, and RENAL nephrometry scores, were retrospectively collected and analyzed to identify statistically significant differences between the two groups.

We used RENAL nephrometry scores for assessing tumor complexity based on computed tomography or magnetic resonance imaging.[12]

RENAL scores were from a quantitative scoring system and the components were radius (R), exophytic/endophytic (E), nearness (N), anterior/posterior (P) and location (L). Perioperative data including approach, operating time, total ischemic time, estimated blood loss, cooling, specimen volume and pathology were recorded. Data on the incidence of complications, new onset of postoperative CKD and eGFR level variation were collected and compared between the two groups. Perioperative complications were defined as those affecting surgical outcomes, and the severity of surgical complications occurring within 1 month after surgery was graded according to the modified Clavien–Dindo Classification system.[13] Renal function was analyzed before the operation and 6 months or 1 year after it in terms of creatinine level and eGFR using the modification of diet in renal disease equation recently modified by the Japanese Society of Nephrology ($eGFR = 194 \times S - creatinine^{1.094}$ mg/dL $\times$ $age^{-0.287} \times 0.739$ [if female]).[14] The stages of CKD are mainly based on measured or estimated GFR. Stage 3 CKD was defined as eGFR <60 mL/min/1.73 m^2. New-onset CKD at 1 year follow up was defined as the number of stage 3 CKD cases newly downgraded from stage 1 or stage 2 CKD. The eGFR loss was the absolute value on subtracting postoperative eGFR from preoperative eGFR.

Surgical technique

The LPN procedure was carried out according to a previously described technique.[15] The choice of approach depended on the location of the tumor. Essential steps include renal defatting, maintaining fat over the tumor, laparoscopic ultrasound to identify the resection line, renal artery clamping with or without renal vein clamping, tumor excision with clod scissors, suture repair of the opened collecting system and continuous parenchymal suturing.

In the case of a retroperitoneal approach, ice-cold saline was used for washing out blood from the wound while incising the renal masses. To prevent renal damage, intravenous injections of 50 mL of 20% mannitol were used before renal artery clamping and after removal of the clamp in all cases. All of the procedures were carried out by a single surgeon (KM), who had extensive experience of urological laparoscopic surgery.

Data analysis

Quantitative parameters were compared using Student's *t*-test, and qualitative parameters were compared using the χ^2-test and Fisher's exact test. Correlations between each parameter were compared using Pearson's product-moment correlation coefficient. Univariate and multivariate logistic regression models were used to determine the variables that were independently correlated with trifecta accomplishment. Variables with *P*-value <0.10 on univariate analysis were used for the creation of a multivariable model. All *P*-values were estimated, and $P < 0.05$ was considered statistically significant. All statistical analyses were carried out with SPSS version 10.1 (SPSS, Chicago, IL, USA).

Results

Of the 63 patients, 39 (62%) achieved trifecta outcomes. The patients' demographic and tumor characteristics are summarized in Table 1. There were no significant differences in age, sex, BMI, ASA score, preoperative CKD, preoperative creatinine, preoperative eGFR, side, RENAL nephrometry score, radius component, exophytic/endophytic component and location component. Preoperative eGFR was slightly better for the trifecta group, but the difference was not significant ($P = 0.092$).

Tumor size, distance from the UCS or sinus, nearness component of RENAL nephrometry score and surgeon's learning curve were significantly different between the two groups.

Perioperative and postoperative outcomes are shown in Table 2. Operating time was not analyzed because of a strong correlation with TIT, as determined using Pearson's correlation coefficient ($r = 0.63$, $P < 0.001$). There were no significant differences in approach, water cooling of the kidney in the retroperitoneal approach and pathological diagnosis. There were no cases of upstaging to pT3a on final pathology and all patients were classified as pathological T1aN0M0. Estimated blood loss ($P < 0.05$) and specimen volume ($P < 0.05$) were significantly different between the two groups.

The incidences of complications, trifecta, CKD and eGFR level variation are shown in Table 3. We observed two complications (one intraoperative and one postoperative) in the 63 cases (3.2%). The intraoperative complication was hemorrhage. The postoperative complication defined as grade 3a in the Clavien–Dindo Classification system was hematuria as a

Table 1 Patient demographic and tumor characteristics

Variables	Trifecta	No. trifecta	Total	*P*-value
No. patients	39	24	63	
Mean age (years)	56.5 ± 10.6	60.2 ± 8.7	57.9 ± 10.2	0.267
Sex (*n*)				0.976
Male	31	19	50	
Female	8	5	13	
Mean BMI (kg/m^2)	24.9 ± 3.2	24.0 ± 2.8	24.7 ± 3.0	0.62
ASA score (*n*)				0.301
1	19	15	4	
2	41	24	17	
3	3	0	3	
Preoperative CKD ≥grade 3 (*n*)	3	4	7	0.491
Median preoperative creatinine, mg/dL (IQR)	0.78 (0.16)	0.83 (0.2)	0.8 (0.18)	0.132
Median preoperative eGFR, mL/min/1.73 m^2 (IQR)	77.2 (17.9)	70.0 (19.2)	76.8 (20.7)	0.092
Side (*n*)				0.708
Left	16	11	27	
Right	23	13	36	
Median tumor size, mm (IQR)	20 (9)	27.5 (7.2)	24 (10.5)	<0.001
Median distance from UCS or sinus, mm (IQR)	6 (4.2)	4 (4.2)	5 (3.5)	<0.001
Median RENAL nephrometry score (IQR)	6 (2)	6 (1)	6 (2)	0.321
4	3	0	3	
5	11	5	16	
6	9	10	19	
7	9	6	15	
8	5	1	6	
9	2	2	4	
Radius component				1
1	39	24	63	
2	0	0	0	
3	0	0	0	
Exophytic/endophytic component				0.223
1	14	14	28	
2	25	10	35	
3	0	0	0	
Nearness component				<0.05
1	13	13	26	
2	15	11	26	
3	11	0	11	
Location component				0.375
1	21	17	38	
2	12	4	16	
3	6	3	9	
Surgeon's learning curve				<0.01
≦30 (*n*)	13	17	30	
>30 (*n*)	26	7	33	

result of arteriovenous fistula, which was treated by transcatheter arterial embolization. A transfusion was given intraoperatively in one case. PSM were observed in four cases. There was no postoperative recurrence in these four cases, but one case relapsed among those with a negative surgical margin.

A total of 21 patients had TIT ≥25 min. New-onset postoperative CKD cases numbered four (one case in the trifecta group and three cases in the no trifecta group). At 6-month or 1-year follow up, eGFR losses were 2.0 mL/min/1.73 m^2 in the trifecta group and 4.6 mL/min/1.73 m^2 in the no trifecta group. There were no significant differences between the two groups for preoperative and postoperative CKD, and new-onset postoperative CKD. There was a tendency for better results of eGFR loss (%) at 6-month or 1-year follow up to be seen in the trifecta group, but the differences were not statistically significant. The results of logistic regression analysis showed that tumor size ($P < 0.005$) and surgeon's learning curve ($P < 0.001$) were variables that could predict trifecta outcomes (Table 4).

Discussion

Oncological functional outcomes of PN and nephrectomy have been rated as equivalent in renal tumors of <4 cm, so PN has become the standard treatment. Although the benefits

Table 2 Perioperative and postoperative outcomes

Variables	Trifecta	No. trifecta	Total	*P*-value
No. patients	39	24	63	
Approach (*n*)				0.836
Intraperitoneal	14	8	22	
Retroperitoneal	25	16	41	
Median operating time, min (IQR)	161 (39)	200 (31)	177 (50)	
Median ischemic time, min (IQR)	17 (7.7)	31 (13.5)	21 (11.5)	
Median estimated blood loss, mL (IQR)	44 ± 41	158 ± 167	87 ± 95	<0.05
Median specimen volume (g)	9 (6)	12 (12.3)	10 (10)	<0.05
Cooling (*n*)	25	16	41	0.836
Pathology (*n*)				0.680
Clear cell	30	20	52	
Papillary	5	3	8	
Chromophobe	4	1	5	

Table 3 Incidence of complications, trifecta outcomes, CKD and eGFR level variation

Variables	Trifecta	No. trifecta	Total	*P*-value
No. patients	39	24	63	
Complication	0	2	2	
Intraoperative	0	1	1	
Postoperative Clavien ≥grade 3	0	1	1	
Open conversion (*n*)	0	1	1	
Surgical margin (*n*)	0	4	4	
Postoperative recurrence (*n*)	1	0	0	
TIT >25 min (*n*)	0	21	21	
Preoperative CKD ≥grade 3 (*n*)	3	4	7	0.491
Postoperative CKD ≥grade 3 (*n*)	4	7	11	0.114
New-onset CKD ≥grade 3 at 1 year (*n*)	1	3	4	0.246
Median eGFR loss at 1 year, % (IQR)	2.0 (7.9)	4.6 (10.3)	2.8 (8.5)	0.054

Table 4 Multivariate analysis for trifecta outcome

Variables	Odds ratio	95% CI	*P*-value
Preoperative eGFR	0.976	0.926–1.028	0.357
Tumor size	1.265	1.077–1.486	<0.005
Nearness of UCS	0.760	0.501–1.154	0.198
Surgeon's learning curve	0.020	0.002–0.184	<0.001

of laparoscopic surgery include its lower invasiveness compared with open surgery, there is a possibility that technical difficulties could lead to increased PSM, the onset of complications and worse renal function deterioration. Preserved renal function and surgical margins have been the subject of discussion as indicators to evaluate the outcomes of PN.

In patients with a contralateral normally functioning kidney, the normal kidney might play a role of compensating for the functional damage caused by prolonged ischemia. Renal scintigraphy is superior to eGFR loss in terms of evaluating the loss of function of an operated kidney, and has been used for the assessment of preserved renal function in recent years.[10,11,16]

Thompson *et al.* reported that the quantity of preserved kidney and warm ischemia time (WIT) <25 min affect the incidence of CKD stage 4 in OPN.[11] Funahashi *et al.* reported that irreversible diffuse damage was seen in surgically preserved nephrons when WIT was ≥25 min in OPN.[10] In addition, Porpiglia *et al.* reported that renal dysfunction was prolonged up to 1 year after surgery in renal scintigraphy when WIT was ≥25 min in LPN.[16] Mir *et al.* reported that renal function after PN correlated with parenchymal volume preservation, whereas ischemia played a secondary role as long as it was limited (<25 min) or if hypothermia was applied.[17] Lowering the renal parenchymal temperature to 20–25°C by renal cooling makes it possible to extend the ischemia time of the kidney to more than 2 h.[18] Although several methods have been reported in laparoscopic surgery, these procedures were not widely carried out.[19,20] In the present study, we used TIT <25 min as a surrogate marker of renal function preservation.

The reported rates of intraoperative and postoperative complications for LPN were similar to those of OPN.[21,22] Hilar tumors and tumors located at the cortico-medullary junction were identified as risk factors for surgical complications of LPN.[23] In the present cases, the intraoperative surgical complication was an open conversion as a result of uncontrolled bleeding, and the postoperative Clavien grade 3a complication was gross hematuria in a patient with anticoagulation therapy as a result of arteriovenous fistula treated by embolization.

The reported incidence of PSM for LPN was 0.7–4.4%.[24,25] The predictive factors of PSM for LPN remained unknown, but as imperative indications, small and endophytic tumors were more likely to be PSM for OPN.[26,27] PSM could be an independent risk factor of local recurrence and shorten the time to local recurrence, but did not affect cancer-specific survival and overall survival.[26–28]

Trifecta is a superior concept that can be rapidly used to evaluate functional and oncological outcomes after PN. Trifecta outcomes have already been reported in OPN versus LPN for T1a renal tumor in a multicenter study and LPN versus RAPN for the work of a single surgeon.[5,6] The accomplishment rate of trifecta outcomes in T1a renal masses in LPN was reported to be 74.3% in a multicenter study; Minervini *et al.* reported that it was the same as for OPN defined as WIT <25 min, negative margins and no perioperative complications.[6] Khalifeh *et al.* reported that the rates of trifecta outcomes were 58.7% in RAPN and 31.6% in LPN defined as WIT <25 min, negative margins, and no complications intraoperatively and up to 3 months postoperatively.[5] By comparison of the results in terms of the operative method, Khalifeh *et al.* also found that the trifecta outcomes were superior in RAPN, although the cases for RAPN had higher tumor complexity than the cases for LPN. Recently, Zargar *et al.* reported a new concept of the "optimal outcome," which was pentafecta outcomes defined as the achievement of trifecta plus no CKD upstaging and minimum 90% total eGFR preservation.[29] "Optimal outcome" has a more strict definition for partial nephrectomy and is thought to be widely used.

In the present study, the accomplishment rate of trifecta outcomes in T1a renal tumors was 62%. This is almost equal to the trifecta accomplishment rate previously reported in T1a renal cancer regardless of the type of operation.[4–6] New-onset stage 3–4 CKD patients at 1 year numbered one in the trifecta group and three in the no trifecta group. There was no significant difference in new-onset stage 3–4 CKD between the trifecta group and the no trifecta group ($P = 0.246$). GFR losses at 1 year were 2.0% in the trifecta group and 4.6% in the no trifecta group ($P = 0.054$). Although TIT in the trifecta group was shorter than in the no trifecta group, there was no significant difference in postoperative deterioration of preserved renal function between the trifecta group and the no trifecta group. From these results, we believe there might be a stronger factor other than TIT to determine the postoperative deterioration of preserved renal function.

Among our cases, positive surgical margins were seen in four cases (6.3%), which is a higher rate than previously reported. Intrarenal recurrence was seen in one patient in the trifecta group, while there was no recurrence in the no trifecta group. We carry out additional resection of the tumor bed and coagulate carefully when it is recognized that cutting into the tumor capsule has occurred during surgery. In other reports, it is described that positive surgical margins might not necessarily lead to oncological functional outcomes, so this issue remains controversial.[26] Gorin *et al.* reported that 4.8% of patients who underwent robotic partial nephrectomy for clinical T1 renal masses were upstaged to pT3a and, in particular, 2.8% of cT1a patients were upstaged to pT3a in a multi-institutional analysis.[30] Among our cases, there were no cases of upstaging to pT3a on final pathology.

In multivariate analysis, the predictive factors affecting trifecta outcomes were tumor size and surgeon's learning curve. Surgeon's learning curve was the strongest predictive factor and, after the learning curve, in 30 cases, the risk of no trifecta outcomes was dramatically decreased.

In the present study, there was no correlation between trifecta outcomes and tumor complexity, but the median nephrometry score in LPN was 6. Even in our institution, for cases such as those with high tumor complexity and multiple tumors, OPN is often selected. Therefore, there was a tendency for tumor complexity to be relatively low in the present study. Because moderate- and high-complexity cases, such as embedded tumors and tumors located in the hilum, tended to be subjected to OPN, the correlation of trifecta outcomes and tumor complexity is unknown in the present study.

However, cases with a larger tumor size and limited experience of the surgeon in T1a renal cancer could not achieve trifecta outcomes, so we should recognize that the selection of cases is important to achieve a good outcome.

In recent years, RAPN has spread widely and several reports regarding surgical outcomes of RAPN have been published. Khalifeh *et al.* reported the superiority of RAPN over LPN in a single-surgeon series in terms of a wider range of indications, better operative outcomes and lower perioperative morbidity, as well as a shorter learning curve.[5] Zargar *et al.* reported that RAPN was superior to LPN in terms of surgical outcomes measured by trifecta in a large multi-institutional series.[29] Although LPN and RAPN have achieved NSS with minimal invasiveness, there are large differences in the technical difficulties between the two procedures.

There were several limitations to the present study, including its retrospective nature and small sample size. In our institution, LPN cases were relatively uniform, because high-complexity tumors tended to be subjected to OPN.

In conclusion, the present study shows that tumor size and surgeon's learning curve are predictors of trifecta outcomes in LPN for clinical T1a renal masses. Although the concept of trifecta involves overall functional evaluation in PN, there are still several controversies. PSM is not necessarily correlated with overall survival. There were no significant differences in renal function decline in TIT $\geq$25 min before and after for small-diameter tumors. These issues require further study.

Conflict of interest

None declared.

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Surgical and Oncologic Outcomes of Laparoscopic Partial Nephrectomy: A Japanese Multi-Institutional Study of 1375 Patients

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Abstract

Background and Purpose: Despite clear trends toward minimally invasive surgery, information about laparoscopic partial nephrectomy (LPN) in Japan is sparse. We conducted a retrospective survey to clarify time trends for LPN and analyze surgical and oncologic outcomes.
Patients and Methods: A nationwide survey was performed. Between 1998 and 2008, 1375 patients underwent LPN at 54 institutions. Complications, patterns of tumor recurrence, and recurrence-free survival were analyzed.
Results: Renal pedicle clamping was used in 1031 (75%) cases, and renal cooling was performed in 64%. Median warm/cold ischemic time was 37/53 minutes. Median tumor size was 2.26 cm (interquartile range 1.6 to 2.7). Multivariate analysis identified total operative time, operative blood loss, and surgical margin status as independently associated with high grade (grade 3–5) urologic and nonurologic complications. Despite increases in central tumor, a trend was seen toward shorter warm/cold ischemic time in recent cases, and the overall complication rate did not change throughout the study period. With a median follow-up of 26 months for 1193 malignancies, recurrence occurred in 22 (1.7%) patients, including local recurrence in 7 (0.5%), lung in 8 (0.7%), lymph nodes in 2 (0.1%), and bone in 4 (0.3%). Of the 26 cases with positive surgical margins, local tumor recurrence occurred in only one.
Conclusions: This is the first nationwide survey of LPN in Japan to be reported. LPN could be performed with acceptable positive margins and complication rates. Most tumor recurrences occur as metastases, and surgical margin status appears to have little impact on oncologic outcomes.

Introduction

Radical nephrectomy (RN) is a significant risk factor for the development of chronic kidney disease (CKD).[1] Better understanding of the increased risk of CKD with RN and recent data highlighting associations between CKD and cardiovascular morbidity and mortality have led to the desire to preserve as much normal parenchyma as possible.[2–4] Open partial nephrectomy (OPN) is now the standard surgical treatment for a small renal mass, providing oncologic outcomes equivalent to those with RN.[5,6]

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Table 1. Baseline Clinical Characteristics

Variables	All patients			era1			era2			era3			p Value
	No. Pts.	Data		No. Pts.	Data		No. Pts.	Data		No. Pts.	Data		
Mean ± SD age (IQR)	1373	59.8 ± 12.2	(51–69)	147	60 ± 11.7	(52–69)	622	59.2 ± 12.2	(50–69)	604	60.3 ± 12.2	(53–70)	0.29
Mean ± SD kg/m^2 BMI[a] (IQR)	1372	24 ± 3.5	(21.9–26.1)	146	24 ± 3.2	(21.8–25.8)	622	24 ± 3.3	(21.8–26.0)	604	24 ± 3.9	(21.9–26.4)	0.68
No. gender (%)	1373			147			624			602			0.80
M		975	(71)		105	(71)		448	(72)		422	(70)	
F		398	(29)		42	(29)		176	(28)		180	(30)	
Mean ± SD ASA score	1325	1.56 ± 0.63		146	1.56 ± 0.64		604	1.49 ± 0.58		575	1.66 ± 0.65		< 0.0001
No. hypertension (%)	1374	496	(36.0)	147	44	(30.0)	624	204	(32.7)	603	248	(41.1)	0.002
No. diabetes mellitus (%)	1374	230	(16.7)	147	27	(18.4)	624	75	(12.0)	603	128	(21.2)	< 0.0001
No. hyperlipidemia (%)	1367	175	(12.8)	147	9	(6.1)	620	69	(11.1)	600	97	(16.2)	0.001
Mean ± SD preop serum creatinine (mg/dl) (IQR)	1314	0.82 ± 0.25	(0.7–0.9)	142	0.84 ± 0.26	(0.7–1.0)	587	0.83 ± 0.26	(0.7–0.9)	585	0.81 ± 0.24	(0.7–0.9)	0.45
Mean ± SD preop eGFR (ml/min/1.73m^2)[b] (IQR)	1312	74.1 ± 19.4	(63–86)	142	72.5 ± 20.5	(58–83)	585	74.2 ± 19.4	(64–86)	585	74.5 ± 19.3	(63–86)	0.28
No. preop CKD stage 3 or greater[c] (%)	1312	275	(21)	142	38	(27)	585	120	(21)	585	117	(20)	0.19

[a]body mass index = mass (kg) / (height(m))^2.
[b]eGFR (mL/min/1.73m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female).
[c]eGFR less than 60 ml/min/1.73m^2.
SD = standard deviation; IQR = interquartile range; BMI = body mass index; ASA = American Society of Anesthesiologists; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease.

In an effort to reduce patient morbidity, urologic surgeons have adapted the minimally invasive technique of laparoscopy to kidney removal. Laparoscopic partial nephrectomy (LPN) is associated with somewhat greater ischemia time and postoperative complications compared with OPN.[7] Several technical modifications for LPN have recently been introduced, resulting in improved outcomes and wider adoption.[8,9] Few reports, however, have examined long-term oncologic outcomes for LPN.[10]

Despite a drastic trend toward minimally invasive surgery, data on the prevalence of LPN in Japan and surgical outcomes are sparse. To obtain such information, we conducted a nationwide survey.

Patients and Methods

The Institutional Review Board approved retrospective data collection and reporting of the results for this study. A nationwide survey was performed by the Japanese Society of Endourology LPN study group. A survey was sent to all 473 urologists (228 institutes) certified by the Endoscopic Surgical Skill Qualification System in Urological Laparoscopy.[11] The system was established in 2003 and was designed to certify urologists who have the capability to complete laparoscopic nephrectomy or adrenalectomy safely and appropriately by their own efforts.[11] Institutes in which more than 10 cases of LPN had been performed at the time of survey were eligible for the study. We retrospectively reviewed 1375 patients who underwent LPN between December 1998 and December 2008.

Baseline renal function was evaluated by serum creatinine measurements and calculation of estimated glomerular filtration rate (eGFR), the latter based on the Japanese Society of Nephrology Chronic Kidney Disease Initiative equation: GFR $(mL/min/1.73\,m^2) = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female).[12] Because LPN with pedicle clamping was introduced in Japan around 2002 and the number of LPNs markedly increased from 2007, we divided the 1375 patients into three chronological eras: Era 1, 147 cases from December 1998 to December 2002; era 2, 624 cases from January 2003 to December 2006; and era 3, 604 cases from January 2007 to December 2008.

All complication events occurring within 30 days after surgery were included in the study. A five-tiered classification scheme based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0, was used to grade the intensity of therapy needed for each complication, including: Grade 1, mild adverse event; grade 2, moderate adverse event; grade 3, severe and undesirable adverse event; grade 4, life-threatening or disabling adverse event; and grade 5, death related to adverse event.[13]

Uni- and multivariate logistic regression analyses were used to evaluate variables associated with experiencing a complication, with separate analyses conducted for the outcome of high-grade (grade 3–5) complications. Continuous variables were reported as mean (standard deviation) and range or as median and interquartile range, as appropriate. The Student *t* test and the Wilcoxon rank sum test were used to compare continuous variables, as appropriate. The Pearson chi-square test was used to compare categoric variables. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with the log rank statistic. Univariable and multivariable logistic regression models addressed time after surgery. Statistical significance in this study was set as $P = 0.05$. All reported *P* values were two-sided, and analyses were performed using JMP9® software (SAS Institute, Cary, NC).

Results

Patient demographics

Of the 228 institutes to which surveys were sent, 54 (23.7%) participated in the study, and a total of 1375 patients were enrolled. All of the hospitals that participated were teaching centers certified by the Japanese Urological Association. The median number of cases reported by center was 27 (range 10–102). The median age at the time of LPN was 60 years (range 16–88 y). Distributions of baseline characteristics are summarized in Table 1. Basic characteristics were similar between the three eras with the exception of the American Society of Anesthesiologists score and frequency of diabetes mellitus. Cold ischemic partial nephrectomy (PN) was performed for 657 (48%) cases; 59% of kidneys were cooled with ice-cold saline using an irrigation device, and 41% of kidneys were cooled with ice introduced via a laparoscopic port. A total of 275 (21%) patients had eGFR $< 60\,mL/min/1.73\,m^2$. Patients in the most recent era showed a higher frequency of comorbidity. The number of patients undergoing LPN each year increased with each successive era (Fig. 1).

Perioperative outcomes

The retroperitoneal approach was used in 893 (65%) cases. Pedicle clamping was used in 1031 (75%) cases, and renal cooling was performed in 64% of cases. Median operative time was 245 minutes (Table 2). In era 1, 83% of LPNs were performed without clamping, with three-quarters performed using microwave coagulation[14,15] and the others performed using methods such as bipolar electrocoagulation and ultrasonic scalpels.

To ensure pelvicaliceal repair, a ureteral catheter was inserted cystoscopically into the affected renal pelvis in 910 (66%) patients, and the total operative time included time for catheter insertion.

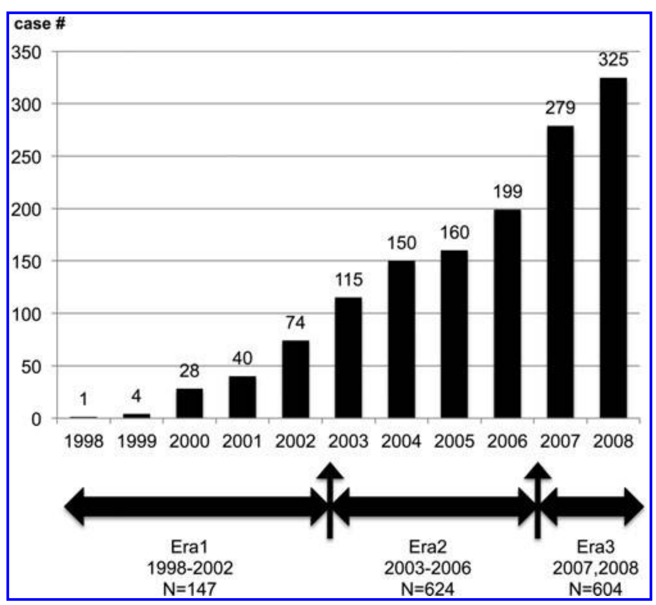


FIG. 1. Patients undergoing laparoscopic partial nephrectomy per era.

Table 2. Perioperative Data

	All patients			era1			era2			era3			
	No. Pts.	Data		No. Pts.	Data		No. Pts.	Data		No. Pts.	Data		p Value
Approach (%)	1372			147			624			604			0.0001
transperitoneal		448	(33)		38	(26)		175	(28)		235	(39)	
retroperitoneal		893	(65)		89	(61)		438	(70)		366	(61)	
HALS[a]		34	(2)		20	(13)		11	(2)		3	(0)	
No. solitary kidney (%)	1373	28	(2)	147	5	(3)	623	15	(2)	603	8	(1)	0.19
No. rt kidney (%)	1360	720	(53)	147	69	(47)	616	328	(53)	597	323	(54)	0.44
No. LPN indication (%)	1310			144			583			583			0.04
imperative		81	(6)		11	(8)		45	(8)		25	(4)	
elective		1229	(94)		133	(92)		538	(92)		558	(96)	
No. interpolar tumor[b] (%)	1372	563	(41)	147	55	(37)	621	243	(39)	604	265	(44)	0.15
No. central tumor (%)	1358	112	(8)	147	6	(4)	618	37	(6)	593	69	(12)	0.0003
Tumor diameter (cm)	1372			146			623			603			0.73
Mean ± SD		2.3 ± 0.9			2.2 ± 0.8			2.3 ± 0.9			2.3 ± 0.9		
Median (IQR)		2	(1.6–2.7)		2	(1.6–2.5)		2	(1.6–2.8)		2	(1.7–2.7)	
Total operative time (min)	1375			147			624			604			0.10
Mean ± SD		259 ± 91			269 ± 106			264 ± 90			251 ± 87		
Median (IQR)		245	(191–313)		240	(189–330)		248	(195–317)		242	(185–307)	
Operative blood loss (ml)	1375			147			624			604			0.01
Mean ± SD		210 ± 426			325 ± 584			202 ± 429			189 ± 370		
Median (IQR)		50	(20–200)		100	(20–330)		52.5	(20–200)		50	(20–200)	
No. pedicle clumping (%)	1375	1031	(75)	147	21	(14)	624	474	(76)	604	536	(89)	< 0.0001
Warm ischemic time (min)	355			12			144			199			0.04
Mean ± SD		41 ± 19			53 ± 23			43 ± 22			38 ± 16		
Median (IQR)		37	(26–50)		50	(36–70)		38	(26–54)		35	(26–48)	
Cold ischemic time (min)	657			7			316			328			0.002
Mean ± SD		56 ± 25			61 ± 20			59 ± 24			54 ± 26		
Median (IQR)		53	(39–70)		58	(50–70)		55	(42–73)		50	(36–66)	
No. calyceal suturing (%)	1342	485	(36)	146	25	(17)	607	211	(35)	589	249	(42)	< 0.0001
No. positive surgical margine (%)	1334	26	(2)	140	2	(1)	602	14	(2)	592	10	(2)	0.65
No. Conversion (%)	1374			147			622			604			0.86
to Open partial nephrectomy		69	(5.0)		7	(4.8)		32	(5.1)		30	(5.0)	
to Open nephrectomy		6	(0.4)		0	(0)		4	(0.6)		2	(0.3)	
to Laparoscopic nephrectomy		27	(2.0)		2	(1.4)		17	(2.7)		8	(1.3)	

[a]Hand-assisted Laparoscopic Surgery (transperitoneal approach).
[b]tumor in middle-third of kidney.
LPN = laparoscopic partial nephrectomy; SD = standard deviation; IQR = interquartile range.

Table 3. Urological Complications

	All patients		era1		era2		era3		
	No. Pts.	Data	No. Pts.	Data	No. Pts.	Data	No. Pts.	Data	p Value
Renal insufficiency (%)	1322		147		588		587		
All Grade		5 (0.4)		0 (0.0)		5 (0.9)		0 (0.0)	0.04
G3. 4		2 (0.2)		0 (0.0)		2 (0.3)		0 (0.0)	0.29
Urine leak (%)	1373		147		622		604		
All Grade		34 (2.5)		7 (4.8)		18 (2.9)		9 (1.5)	0.22
G3. 4		24 (1.7)		5 (3.4)		12 (1.9)		7 (1.2)	0.16
Hematuria (%)	1324		147		590		587		
All Grade		184 (13.9)		27 (18.4)		55 (9.3)		102 (17.4)	<0.0001
G3. 4		17 (1.3)		1 (0.7)		10 (1.7)		6 (1.0)	0.46
Intraop Hemorrhage (%)	1322		147		588		587		
All Grade		115 (8.7)		24 (16.3)		36 (6.0)		55 (9.4)	0.00
G3. 4		31 (2.3)		5 (3.4)		11 (1.9)		15 (2.6)	0.50
Postop Hemorrhage (%)	1369		147		619		603		
All Grade		40 (2.9)		2 (1.4)		21 (3.4)		17 (2.8)	0.41
G3. 4		22 (1.6)		1 (0.7)		10 (1.6)		11 (1.8)	0.61

All complications were classified based on the NCI-CTC version 2.0.

Median warm ischemia time progressively shortened, at 50 minutes, 38 minutes, and 35 minutes in eras 1, 2, and 3, respectively. Median cold ischemic time, including an initial cooling time of about 10 minutes, was 58 minutes, 55 minites. and 50 minutes, respectively. Mean eGFR at baseline and 12 months after LPN were 74.1 and 65.8 mL/min/1.73 m^2, respectively, and the difference was significant ($P<0.0001$). LPN was successfully completed as planned in 1271 (92.6%) patients. Conversion to OPN, open nephrectomy, and laparoscopic nephrectomy occurred in 69 (5.0%), six (0.4%), and 27 (2.0%) cases, respectively.

Early complications

Table 3 lists urologic complications. Grade 3/4 urologic complications comprised renal insufficiency in four (0.3%)/2 (0.2%), urine leakage in 34 (2.5%)/24 (1.7%), hematuria in 182 (13.8%)/17 (1.3%), and hemorrhage in 115 (8.7%)/31 (2.3%) cases. Postoperative hemorrhage was seen in 40 (2.9%) cases, 14 (1.0%) of which necessitated transcatheter arterial embolization. Blood transfusion was needed in 21 (1.5%) patients. With regard to nonurologic complications, grade 3–5 complications arose in four patients, comprising one pulmonary embolism, one ascending colon injury on insertion of the port, one cerebral infarction, and one air embolism that occurred during the use of fibrin glue (Bolheal,® The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) and resulted in death (grade 5) on postoperative day 7.

On univariate analysis, body mass index, hypertension, tumor diameter (cm), total operative time (min), operative blood loss (mL), caliceal suturing, and surgical margin status were significantly associated with high-grade (grades 3–5) complications (Table 4). Factors that lacked significance were age, sex, hyperlipidemia, preoperative renal function (creatinine, eGFR), indication of LPN, solitary kidney, renal cooling, pedicle clamping.

On multivariate analysis, total operative time (min), operative blood loss (mL), and surgical margin status were independently associated with grade 3 to 5 complications.

Pathologic findings and oncologic outcomes

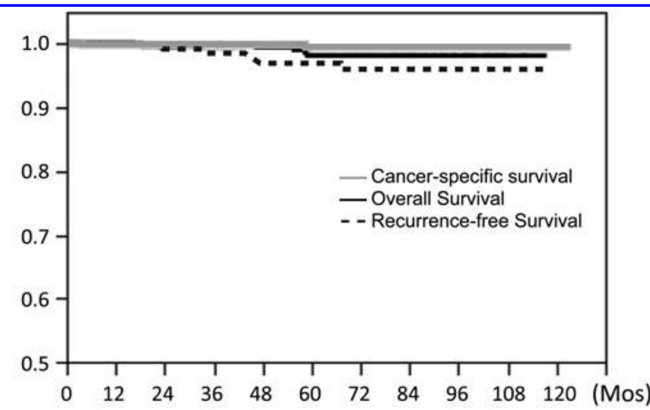
Of the 1375 LPN in our dataset, 182 (13.2%) were associated with benign lesions, including angiomyolipoma in 109 (7.9%), oncocytoma in 30 (2.2%) and others in 43 (3.1%). Malignant histology was found in 1193 (86.8%) cases, including clear cell carcinoma in 1049 (76.3%), papillary carcinoma in 95 (6.9%), chromophobe carcinoma in 36 (2.6%), and others in 13 (0.9%).

With a median follow-up of 26 months for 1193 patients with malignant histology, recurrence occurred in 23 (1.7%)

Table 4. Univariate and Multivariate Analyses for Predicting Grade 3-5 Complications

	Univariate			Multivariate		
	HR	95% CI	p Value	HR	95% CI	p Value
BMI	1.063	(1.015, 1.114)	0.009	1.004	(0.938, 1.075)	0.91
hypertension	1.426	(1.013, 2.000)	0.04	1.143	(0.742, 1.749)	0.54
preop CKD	1.511	(1.012, 2.218)	0.04	1.389	(0.865, 2.189)	0.17
Tumor diameter (cm)	1.480	1.257, 1.740)	<0.001	1.131	(0.920, 1.379)	0.24
Total operative time (min)	1.007	(1.005, 1.008)	<0.001	1.003	(1.000, 1.006)	0.04
Operative blood loss (ml)	1.001	(1.001, 1.002)	<0.001	1.001	(1.001, 1.002)	<0.0001
calyceal suturing	1.733	(1.227, 2.444)	0.002	1.444	(0.955, 2.181)	0.08
positive surgical margin	4.696	(1.966, 10.517)	0.001	3.498	(1.246, 8.872)	0.02

BMI = body mass index; CKD = chronic kidney disease.



	1-year	2-year	3-year	5-year	8-year
Cancer-specific Survival	99.9	99.9	99.9	99.5	99.5
No. at risk	979	685	476	211	32
Overall survival	99.8	99.6	99.6	98.6	97.5
No. at risk	979	685	476	211	32
Recurrence-free Survival	99.5	99.1	98.0	95.9	95.1
No. at risk	974	677	466	204	31

FIG. 2. Survival in 1193 patients with malignant history.

patients (Fig. 2), including local recurrence in seven (0.5%), lung in eight (0.7%), lymph nodes in two (0.1%), and bone in four (0.3%). Tumor recurrence rate according to tumor size was 0.0% for 0 to 1.0 cm tumors (n = 14), 0.3% for 1.1 to 2.0 cm (n = 382), 0.8% for 2.1 to 3.0 cm (n = 524), and 0.8% for tumors > 3 cm (n = 247). On univariate analysis, tumor size was not significantly associated with recurrence rate ($P = 0.145$). Positive surgical margins were observed in 26 cases, in which 22 (85%) involved malignancy; eight were converted to laparoscopic RN, and recurrence occurred in only one case.

Nine patients died during the study period. After excluding the patient who died 7 days postoperatively because of pulmonary embolism, the remaining eight cases were analyzed. Mean time to death after LPN was 39 months. Two patients died from kidney cancer; one in whom lung metastases had been identified preoperatively died 59 months after LPN, and one died 4 months after surgery because of intraperitoneal recurrence. Four patients died from other malignancies (Fig. 2).

Discussion

PN was initially reserved for absolute indications such as patients with a solitary kidney, renal insufficiency that would likely result in the need for dialysis, or inheritable forms of renal cancer. PN, however, is now considered the treatment of choice for most clinical T1 renal masses, even in patients with a normal contralateral kidney. With advances in laparoscopic instrumentation and greater dissemination of expertise, LPN is now often performed using the same surgical techniques as its open counterpart, such as vascular control,[9] renal hypothermia,[8] watertight closure of the collecting system and capsule, and use of surgical bolsters. With these advances, LPN has gained popularity as a less-invasive procedure for small renal tumors. In particular, patients with small peripheral lesions who meet the criteria for OPN should be considered for LPN.

To facilitate standardized comparisons among cohorts, we classified complications based on NCI-CTC, version 2.0. This allowed systematic and comprehensive reporting of surgical complications by standardizing definitions of complication events and enabling clear comparison of the frequency and severity of events among various series.[16] We compared our LPN data with reported series that had used the same standardized NCI-CTC reporting method.[17] All-grade complication rates were 8% to 18% and 27% for urologic complications, and 11% to 15% and 2% for nonurologic complications in previous reports and the present study, respectively.

The present study appeared to have higher rates of low-grade hematuria and intraoperative hemorrhage, but this cohort included many institutes, and some events might have been overclassified in the retrospective chart review, especially for hematuria and intraoperative hemorrhage. Regarding high-grade events, the present data were comparable to other reports. Postoperative hemorrhage is arguably the most important urologic complication after OPN or LPN. The incidence of hemorrhage is 1.4% to 7.9% after OPN[5] and 2.1% to 6% after LPN.[16,18] Our retrospective cohort contained our initial experience, but the postoperative hemorrhage rate was 2.9% and the urine leakage rate was 2.5%, both of which were comparable to that of previous studies.

On multivariate analysis, only total operative time (min), operative blood loss (mL), and surgical margin status were independently associated with all types of complications. These results were expected, because intraoperative bleeding makes the procedure difficult to perform.

With regard to conversion rate, LPN showed the highest rate (3.9%) among the various procedures, but this rate was still comparable to those for cryoablation (3.5%) and laparoscopic RN (3.0%).[19] In addition, Breda and associates [20] reported the results of 855 LPNs from 17 centers and identified a 2.4% positive margin rate. Our conversion rate was slightly higher (7.4%), but the positive margin rate was only 2%, a figure comparable to previous studies.

As for oncologic outcomes, previous reports have suggested that the presence of a positive surgical margin has no impact on overall or cancer-specific survival for patients treated using PN.[21,22] Reported positive surgical margin rates have varied from 2% to 6% in contemporary OPN and LPN series, while recurrence rates range between 0% and 6%.[23,24] Several reasons might explain such low rates of local recurrence. First, false-positive margins can occur during tissue processing, and even legitimate microfoci of residual cancer cells may never result in clinical recurrence if adequately treated by intraoperative fulguration or application of an argon beam to the tumor base. Second, because the average annual growth rate of radiographically visible but small renal masses is 0.28 to 0.42 cm,[25,26] residual cancer cells may need many years to become clinically apparent. Third, among the cases with tumor recurrence, local recurrence alone developed in only five (23%), and metastasis with or without local recurrence developed in others, indicating that the majority of cases in which recurrence developed already had micrometastases present by the time of surgery. These results should encourage urologists to perform PN, even if the anticipated resection margin is close and the tumor abuts the collecting system or renal hilum.

In this survey, no recurrence was observed for tumors $\leq$1 cm in diameter. Although no significant difference was seen, tumors >2 cm in diameter had a tendency to recur more frequently than those $\leq$2 cm in diameter.

The limitations of our study include the retrospective nature of the data analysis. Each institute has different indications for LPN, so some selection bias likely contributed to the observed differences in rates of complications among institutes. Because the data were based on findings from only 54 institutes, however, some bias might be associated with the results. Because our survey was sent to only urologists certified by the Endoscopic Surgical Skill Qualification System in Urological Laparoscopy, the results are considered to represent the contemporary status of LPN in Japan. Although we should report surgical complications using the Clavien system,[27] we planned this study on 2008, and at that time NCI-CTC, version 2.0, was used as a recommended PN reporting criteria.[17] For the same reason, we could not report anatomic tumor characteristics according to the R.E.N.A.L. (radius; exophytic/endophytic; nearness; anterior/posterior; location) nephrometry score [28] or PADUA (preoperative aspects and dimensions used for an anatomical) score.[29] A prospective study needs to use the scoring system that is an important predictor of perioperative complications and oncologic outcomes.

The present study is unique in that renal cooling was used in about half of the cases. Renal cooling, either by ice or ice-cold saline, has been widely used for LPN in Japan. The limitation, however, is the lack of detailed data on the methods of renal cooling and on split renal function, and of a group receiving OPN. We were thus unable to fully elucidate the impact of LPN alone or LPN with renal cooling on renal function in comparison with open surgery. Becker and colleagues[30] suggested that renal scintigraphy with ^{99m}Tc-mercapto-triglycylglycine is currently the best method for exact determination of renal function loss after tissue resection and ischemic injury. A prospective multi-institutional study comparing the impact of LPN or OPN on split renal function is ongoing and will provide an accurate reflection of the functional status of the operated kidney.

Conclusions

LPN is a challenging surgery necessitating advanced laparoscopic techniques. Using a large cohort and standardized NCI-CTC reporting system, we demonstrated that LPN could be performed with positive margins and complication rates comparable to those of previous studies. Standardization of data reporting will allow for more objective assessment of changes in technique as well as improved comparison of alternative treatment strategies. Most of the tumor recurrences occurred as metastases with or without local recurrence, and surgical margin status appears to have little impact on oncologic outcome.

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Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
LPN = laparoscopic partial nephrectomy
NCI-CTC = National Cancer Institute Common Toxicity Criteria
OPN = open partial nephrectomy
PN = partial nephrectomy
RN = radical nephrectomy