Laparoscopic Adrenalectomy for Metachronous Metastases After Ipsilateral Nephrectomy for Renal-Cell Carcinoma

E. Jason Abel, M.D.,^{1,2} Jose A. Karam, M.D.,¹ Alonso Carrasco, M.D.,¹ and Surena F. Matin, M.D.¹

Abstract

Background and Purpose: While laparoscopic adrenalectomy (LA) is considered the standard of care for removal of small adrenal masses, there are minimal data describing the feasibility and outcomes of LA after previous ipsilateral nephrectomy (PIN). The purpose of the study was to describe the perioperative outcomes in a series of patients who were undergoing LA after PIN.

Patients and Methods: Using an institutional database, we identified patients who underwent LA since 2002 by a single surgeon. Clinical and pathologic data were collected and analyzed. To evaluate outcomes, patients undergoing LA after PIN were compared with patients undergoing LA without PIN.

Results: Of 54 consecutive patients undergoing LA, 8 had PIN for renal-cell carcinoma (RCC). Estimated blood loss was not significantly greater in patients with PIN: 50 mL *vs* 100 mL, $P=0.109$. Operative time was longer in patients with PIN: 120 minutes *vs* 156 minutes, $P=0.015$. There was no difference in length of hospital stay between groups: Median 2 days for both groups, $P=0.635$. One patient in the PIN group had a conversion to open adrenalectomy and needed blood transfusion. Perioperative complications were seen in 5/46 (10.6%) patients without and in 1/8 (12.5%) patients with PIN. Surgical margins were negative in all patients.

Conclusions: To the authors' knowledge, this study represents the largest experience with adrenalectomy in the reoperative setting. LA after PIN is associated with a longer operative time. While the potential for conversion is possible, it is technically feasible in selected patients and thus far appears to be associated with similar perioperative outcomes compared with patients without PIN.

Introduction

SURGICAL RESECTION OF metastases from renal-cell carcinoma (RCC) remains a valid option in the era of targeted molecular therapies, especially as accumulating data show that complete responses are rare with these new agents.¹ Several small series have noted the association between metastasectomy and prolonged survival^{2,3} independent of other known risk factors,⁴ although patients with a good performance status and a solitary site of metastasis or low volume disease appear to be ideal candidates for metastasectomy. Therefore, surgery may be recommended to patients with metachronous ipsilateral adrenal metastasis^{5,6} either with or in the absence of systemic therapy.

Laparoscopic adrenalectomy (LA) is considered the standard of care for patients with small adrenal masses.⁷ In patients who have undergone previous ipsilateral radical or partial nephrectomy (PIN), laparoscopic approaches may not be considered because of obliteration of the retroperitoneal landmarks, intraperitoneal adhesions, and scarring at the potential operative site. In addition, several series of patients

with locally recurrent tumors after PIN have suggested increased morbidity with reoperation.⁸

The purpose of this article was to review our experience with and describe the perioperative outcomes of patients who were undergoing laparoscopic adrenalectomy for metastatic RCC (mRCC) after PIN.

Patients and Methods

We reviewed the medical records of all patients who had undergone LA by a single surgeon and identified patients with adrenal metastases from RCC and PIN. Clinical and pathologic data were collected for each patient. Institutional Review Board approval was granted for this retrospective study.

To evaluate perioperative outcomes, patients undergoing LA for mRCC after PIN were compared with all patients who underwent LA. Continuous variables were summarized using the median and range, and compared using the Mann-Whitney *U* test for nonparametric variables. Categorical variables were compared using the chi-square test, or Fisher exact

¹Department of Urology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas.

²Department of Urology, University of Wisconsin, Madison, Wisconsin.

This study was presented at the World Congress of Endourology Annual Meeting 2010

test when appropriate. SPSS version 17 was used for all statistical analyses.

Surgical technique

The technique of LA is well described and may be performed using a transperitoneal or retroperitoneal approach.⁹ In patients who have undergone nephrectomy, however, the retroperitoneum is obliterated. Therefore, a lateral transperitoneal approach is used for all patients with PIN. Positioning of the patient is more lateral (about 70–90-degree lateral decubitus position), similar to the lateral peritoneal approach as described by Shichman and associates.¹⁰ This provides certain advantages—namely, greater retraction of bowel by gravity, avoidance of most intraperitoneal adhesions (which are usually, but not always, more medially located), and a more direct approach to the adrenal gland. Trocars are placed as per routine LA except more laterally, consisting of one 5- or 12-mm port for the dominant hand and one 12-mm port for the camera, and additional 3-mm, 5-mm, or 12-mm port placed for the nondominant hand, a 3-mm or 5-mm port for lateral retraction for the kidney (in selective cases), and, in right-sided cases, a 3-mm or 5-mm port for retraction for the liver.

A key aspect of dissection in patients undergoing LA in the setting of PIN is the liberal use of sharp dissection with endoshears. Just as in open surgery, blunt dissection is avoided in reoperative planes because it can lead to injury of normal organs, dissection into incorrect tissue planes, and potentially tumor violation. Because of the obliterated planes and varied landmarks, laparoscopic ultrasonography is also used liberally. This is performed after elevation of the liver (right side) or mobilization of the splenic flexure and spleen (left side), but before dissection is performed in proximity to the tumor. These maneuvers allow for orientation of the reoperative anatomy and recognition of any critical landmarks on the right side, such as the vena cava, renal artery, and vein stumps, as well as the tumor (which may be difficult to visually identify in those with a small mass surrounded by copious periadrenal fat); on the left side, ultrasonography can aid with identification of critical structures, such as the pancreatic tail, splenic artery, aorta, and celiac axis. The echogenic location of clips and staples is correlated with available axial scans to reinforce the correct orientation (Figs 1, 2).

Just as with standard LA, a 5-mm bipolar vessel sealing system (Ligasure Atlas, Covidien Corp, Mansfield, MA) was used routinely for dissection of vascular structures. In PIN patients, the remnant stumps of the renal artery and vein were usually clipped more proximally and the more distal segments resected *en bloc* with the adrenal tumor to ensure negative surgical margins, because the medial limb of the adrenal is typically in close approximation or densely adherent to these structures. The adrenal vein was controlled using a single 5-mm polymer locking clip placed proximally (Teleflex Medical, Research Triangle Park, NC), then sealed and divided using the LigaSure.

Results

From 2002 to 2010, LA was performed in 54 patients by a single surgeon. In eight patients, LA was performed for metachronous adrenal mRCC after PIN. The median time from nephrectomy to adrenalectomy was 57 months (17–246 mos). In all patients, biopsy establishing recurrence was performed,

FIG. 1. CT shows a metachronous 3-cm right adrenal metastasis in a 58-year-old patient who underwent radical nephrectomy for renal-cell carcinoma several years previously. Previous clips are evident.

but was nondiagnostic in one patient. Patient characteristics and perioperative results for each group are displayed in Table 1. Two patients underwent bilateral adrenalectomy in the PIN group, one of whom also underwent cholecystectomy; perioperative results for these patients include all performed procedures. All surgical margins after LA were negative in each group. All patients who underwent LA after PIN had surgical pathologic evaluation that demonstrated mRCC. In LA patients without PIN, pathologic evaluation demonstrated adrenal adenoma or benign findings in 22 patients, mRCC in 8 patients, other metastatic primary cancer in 8 patients, pheochromocytoma in 5 patients, and ganglioneuroma in 3 patients. Table 2 summarizes patient characteristics and pathology at the time of LA after PIN.

FIG. 2. Intraoperative ultrasonography shows an adrenal gland (arrowheads) containing a renal-cell carcinoma metastasis (arrows).

TABLE 1. DEMOGRAPHIC VARIABLES IN PATIENTS UNDERGOING LAPAROSCOPIC ADRENALECTOMY

Variable	No previous nephrectomy (n=46)	Previous nephrectomy (n=8)	P value
Age (years)	59.5 (18–81)	67.5 (57–70)	0.045
BMI (kg/m ²)	29.8 (18.7–60.3)	30.82 (20.7–39.4)	0.960
Tumor size (cm)	3.25 (1–11)	2.7 (1–4)	0.695
Length of follow-up	11.5 (0–73)	29.0 (1–74)	0.244
Sex			0.248
Male	29	3	
Female	17	5	
Race			0.563
White	34	8	
African-American	5	0	
Hispanic	6	0	
Asian	1	0	
ASA			0.755
2	12	1	
3	32	7	
4	2	0	
Side			0.026
Left	25	3	
Right	21	3	
Bilateral*	0	2	
Approach			0.176
Retroperitoneal	12	0	
Transperitoneal	34	8	
Estimated blood loss, mL	50 (10–1100)	100 (20–2125)	0.109
Surgery time, min.	120 (60–240)	180 (126–504)	0.015
Length of hospitalization, days	2 (1–6)	2 (1–13)	0.635

*Patients undergoing bilateral adrenalectomy had a virginal operation on one side and previous nephrectomy on the other side. All results include the total operative parameters for both operations.

ASA = American Society of Anesthesiology score; BMI = body mass index.

Estimated blood loss was similar in patients with PIN ($P=0.109$). Operative time was longer in patients with PIN: Median 156 minutes *vs* 120 minutes ($P=0.015$). There was no difference in length of hospital stay between groups: Median 2 days for each group ($P=0.635$).

One patient in the PIN group had a conversion to open adrenalectomy, while there were no conversions in patients without PIN. This patient underwent bilateral adrenalectomy as well as cholecystectomy. Conversion occurred because of

splenic bleeding and prohibitive dense left-sided adhesions in the area of PIN. The single case of blood transfusion and highest blood loss, operative time, and hospitalization was in this one patient. Perioperative complications were seen in 1/8 (12.5%) of patients with PIN and 5/46 (10.6%) of patients without PIN. Complications in patients without PIN included pneumonia, port-site hernia, syncope, superficial wound infection, and urinary tract infection. Four patients in the PIN group achieved complete remission (CR) and had

TABLE 2. OUTCOMES OF PATIENTS UNDERGOING LAPAROSCOPIC ADRENALECTOMY AFTER PREVIOUS IPSILATERAL NEPHRECTOMY FOR RENAL-CELL CARCINOMA

Sex	Age	ECOG PS	Previous nephrectomy approach	Nephrectomy pathology and Fuhrman grade	Time from nephrectomy to LA (mos)	Time from LA to last follow-up (mos)	Condition at last follow-up
F	68	1	Open, flank	ccRCC, Gr3	73	7	Dead, NED
F	58	0	Open, subcostal	ccRCC, Gr2	117	74	Alive with disease
M	62	0	Laparoscopic, hand assisted	ccRCC, Gr4	52	37	Dead of disease
F	70	0	Open, midline	ccRCC, Gr3	50	25	Dead of disease
F	71	0	Open, flank	ccRCC, Gr3	63	34	Alive, NED
F	71	0	Open subcostal	RCC	246	23	Alive with disease
M	70	0	Laparoscopic	ccRCC, Gr3	42	18	Alive, NED
M	67	0	Open partial	ccRCC, Gr3	17	1	Alive, NED

ECOG PS, Eastern Cooperative Oncology Group performance status; LA = laparoscopic adrenalectomy; ccRCC, clear-cell renal-cell carcinoma; Gr, Fuhrman nuclear grade; NED, no evidence of disease.

no evidence of disease at last follow-up without any additional systemic therapy (Table 2).

Discussion

Despite increased survival and improved response rates that are associated with the use of targeted therapies for mRCC, the median overall survival continues to be less than 2 years, with CR being seen rarely.¹ After nephrectomy, however, the time course of metastatic disease progression is variable,¹¹ with some patients progressing quickly while other patients slowly progress or stabilize with low volume metastasis. Patients with mRCC who are otherwise healthy and have oligometastatic disease often undergo metastasectomy because they can achieve surgical CR and a prolonged disease-free interval. Although several series have noted the association of surgical resection of metastases with improved survival,²⁻⁴ it is difficult to prove the survival benefit of surgery, given that these patients are highly selected. In addition, even with known prognostic factors, it is not straightforward which patients will benefit from metastasectomy.

Adrenal metastases after nephrectomy are rare,¹² and adrenalectomy to remove metastases has been associated with prolonged survival.¹³ The cancer-specific survival of 71.4% at 24 months median follow-up is comparable to previous published results showing 51% to 88% survival in patients with intermediate and high-risk disease undergoing metastasectomy.¹¹

Reoperation after ipsilateral nephrectomy has been associated with significant morbidity in patients with renal fossa recurrence,⁸ although a recent report demonstrated laparoscopic resection of RCC recurrence had low morbidity and minimal complications in four patients.¹⁴ In patients with adrenal metastases after nephrectomy, open adrenalectomy necessitates a large incision to gain access for removal of a small gland. In addition to the possible benefits of less pain and a quicker recovery, patients may be able to return to systemic therapy for mRCC faster when using laparoscopic techniques compared with open surgery. Similarly, percutaneous ablation of metastatic sites may offer advantages in recovery time, although there are minimal data for use in mRCC currently.^{15,16} Recovery time is an important consideration, because agents are frequently withheld after surgery because of concerns with wound healing while receiving therapies that are targeting angiogenic pathways.¹⁷

In the current series, the overall rate of complications is low and compares favorably with similar series.^{14,18} The only complication in the reoperative group was one case of hemorrhage resulting in conversion to an open procedure and blood transfusion. The possibility of conversion to open surgery is a key aspect of preoperative patient counseling, because this risk may be higher than in patients without PIN. Finally, the median length of hospital stay of 2 days was not different between groups and comparable to other studies.¹⁹ The longer operation time is likely a result of more time spent in the lysis of adhesions and sharp dissection through obliterated planes.

The surgical approach for LA can be through a transperitoneal or retroperitoneal approach with similar outcomes for small adrenal masses without PIN.⁹ For patients after PIN, a lateral transperitoneal approach^{10,20} is preferred with early

identification of landmarks using ultrasonography when necessary for reasons described earlier.

In the classical description of a radical nephrectomy for RCC, Robson and colleagues²¹ suggested that adrenalectomy should be performed as an integral part of the surgery. Modern series, however, have not shown a benefit to routinely removing the adrenal gland with radical nephrectomy.²² The adrenal gland may become involved by local extension, lymphatic, or hematogenous metastasis with a 1% to 5% incidence of synchronous metastasis.²³ While the risk of adrenal insufficiency is low with concurrent adrenalectomy, the low incidence of adrenal metastasis does not justify removal in all patients. At our institution, adrenalectomy is routinely performed in patients with radiographic suspicion of adrenal involvement, clinical T₂ (>7 cm) or higher stage renal tumors, and upper pole tumors.

To our knowledge, the current series is the largest report demonstrating the feasibility of LA after PIN. In our data, LA is associated with similar perioperative morbidity and outcomes, with a reasonable expectation based on the limited data that there may be a higher rate of conversion to open surgery. Possible weaknesses of this study include its retrospective nature. Given the rarity of the clinical scenario where LA after PIN is indicated, we believe it is an appropriate methodology for this type of report. In addition, we acknowledge that patients are carefully selected for this approach, and the surgeon who performs this procedure should be experienced in standard LA as well as reoperative open and laparoscopic surgery.

At our institution, patients with solitary adrenal metastasis are routinely offered a laparoscopic approach at the discretion of the attending physician. Body habitus, especially elevated body mass index (BMI), and previous surgery may influence a surgeon's decision on type of approach. In the current series, the patients with PIN had a higher median BMI. LA may be technically feasible in selected patients after PIN for mRCC and is associated with similar perioperative outcomes compared with patients without previous nephrectomy.

Acknowledgment

This research is supported in part by the National Institutes of Health through M.D. Anderson Cancer Center Support Grant CA016672.

Disclosure Statement

No competing financial interests exist.

References

1. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. *J Clin Oncol* 2009;27:5794-5799.
2. Göğüs C, Baltacı S, Bedük Y, et al. Isolated local recurrence of renal cell carcinoma after radical nephrectomy: Experience with 10 cases. *Urology* 2003;61:926-929.
3. Itano NB, Blute ML, Spotts B, Zincke H. Outcome of isolated renal cell carcinoma fossa recurrence after nephrectomy. *J Urol* 2000;164:322-325.
4. Eggener SE, Yossefowitch O, Kundu S, et al. Risk score and metastasectomy independently impact prognosis of patients with recurrent renal cell carcinoma. *J Urol* 2008;180:873-878.

5. Dinney CP, Awad SA, Gajewski JB, et al. Analysis of imaging modalities, staging systems, and prognostic indicators for renal cell carcinoma. *Urology* 1992;39:122–129.
6. Griffin N, Gore ME, Sohaib SA. Imaging in metastatic renal cell carcinoma. *AJR Am J Roentgenol* 2007;189:360–370.
7. Kebebew E, Siperstein AE, Duh QY. Laparoscopic adrenalectomy: The optimal surgical approach. *J Laparoendosc Adv Surg Tech A* 2001;11:409–413.
8. Master VA, Gottschalk AR, Kane C, Carroll PR. Management of isolated renal fossa recurrence following radical nephrectomy. *J Urol* 2005;174:473–477.
9. Rubinstein M, Gill IS, Aron M, et al. Prospective, randomized comparison of transperitoneal versus retroperitoneal laparoscopic adrenalectomy. *J Urol* 2005;174:442–445.
10. Shichman SJ, Herndon CD, Sosa RE, et al. Lateral transperitoneal laparoscopic adrenalectomy. *World J Urol* 1999;17:48–53.
11. Eggener SE, Yossepowitch O, Pettus JA, et al. Renal cell carcinoma recurrence after nephrectomy for localized disease: Predicting survival from time of recurrence. *J Clin Oncol* 2006;24:3101–3106.
12. Saitoh H, Nakayama M, Nakamura K, Satoh T. Distant metastasis of renal adenocarcinoma in nephrectomized cases. *J Urol* 1982;127:1092–1095.
13. Antonelli A, Cozzoli A, Simeone C, et al. Surgical treatment of adrenal metastasis from renal cell carcinoma: A single-centre experience of 45 patients. *BJU Int* 2006;97:505–508.
14. Yohannan J, Feng T, Berkowitz J, et al. Laparoscopic resection of local recurrence after previous radical nephrectomy for clinically localized renal-cell carcinoma: Perioperative outcomes and initial observations. *J Endourol* 2010;24:1609–1612.
15. Mouracade P, Dettloff H, Schneider M, et al. Radiofrequency ablation of solitary adrenal gland metastasis from renal cell carcinoma. *Urology* 2009;74:1341–1343.
16. Wang Y, Liang P, Yu X, et al. Ultrasound-guided percutaneous microwave ablation of adrenal metastasis: Preliminary results. *Int J Hyperthermia* 2009;25:455–461.
17. Margulis V, Matin SF, Tannir N, et al. Surgical morbidity associated with administration of targeted molecular therapies before cytoreductive nephrectomy or resection of locally recurrent renal cell carcinoma. *J Urol* 2008;180:94–98.
18. Bandi G, Wen CC, Moon TD, Nakada SY. Single center preliminary experience with hand-assisted laparoscopic resection of isolated renal cell carcinoma fossa recurrences. *Urology* 2008;71:495–500.
19. Lee J, El-Tamer M, Schiffner T, et al. Open and laparoscopic adrenalectomy: Analysis of the National Surgical Quality Improvement Program. *J Am Coll Surg* 2008;206:953–961.
20. Duh QY, Siperstein AE, Clark OH, et al. Laparoscopic adrenalectomy. Comparison of the lateral and posterior approaches. *Arch Surg* 1996;131:870–876.
21. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *J Urol* 1969;101:297–301.
22. O'Malley RL, Godoy G, Kanofsky JA, Taneja SS. The necessity of adrenalectomy at the time of radical nephrectomy: A systematic review. *J Urol* 2009;181:2009–2017.

Address correspondence to:

Surena F. Matin, M.D.

Department of Urology - Unit 1373

UT M.D. Anderson Cancer Center

1515 Holcombe Boulevard

Houston, TX 77030

E-mail: surmatin@mdanderson.org

Abbreviations Used

BMI = body mass index

CR = complete remission

PIN = previous ipsilateral nephrectomy

LA = laparoscopic adrenalectomy

mRCC = metastatic renal-cell carcinoma

RCC = renal-cell carcinoma