Management of the Adrenal Gland During Partial Nephrectomy

Brian R. Lane,*† Ho-Yee Tiong,‡ Steven C. Campbell,§ Amr F. Fergany,‡ Christopher J. Weight,‡ Benjamin T. Larson,‡ Andrew C. Novick‡ and Stuart M. Flechner\| From the Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio

**Purpose:** Nephron sparing surgery is an increasingly used alternative to Robson’s radical nephroadrenalectomy. The indications for adrenalectomy in patients undergoing partial nephrectomy are not clearly defined and some surgeons perform it routinely for large and/or upper pole renal tumors. We analyzed initial management and oncological outcomes of adrenal glands after open partial nephrectomy.

**Materials and Methods:** Institutional review board approval was obtained for this study. During partial nephrectomy the ipsilateral adrenal gland was resected if a suspicious adrenal nodule was noted on radiographic imaging, or if intraoperative findings indicated direct extension or metastasis.

**Results:** Concomitant adrenalectomy was performed in 48 of 2,065 partial nephrectomies (2.3%). Pathological analysis revealed direct invasion of the adrenal gland by renal cell carcinoma (1), renal cell carcinoma metastasis (2), other adrenal neoplasms (3) or benign tissue (42, 87%). During a median followup of 5.5 years only 15 patients underwent subsequent adrenalectomy (0.74%). Metachronous adrenalectomy was ipsilateral (10), contralateral (2) or bilateral (3), revealing metastatic renal cell carcinoma in 11 patients. Overall survival at 5 years in patients undergoing partial nephrectomy with or without adrenalectomy was 82% and 85%, respectively (p \(0.56\)).

**Conclusions:** Adrenalectomy should not be routinely performed during partial nephrectomy, even for upper pole tumors. We propose concomitant adrenalectomy only if a suspicious adrenal lesion is identified radiographically or invasion of the adrenal gland is suspected intraoperatively. Using these criteria adrenalectomy was avoided in more than 97% of patients undergoing partial nephrectomy. Even using such strict criteria only 13% of these suspicious adrenal nodules contained cancer. The rarity of metachronous adrenal metastasis and the lack of an observable benefit to concomitant adrenalectomy support adrenal preservation during partial nephrectomy except as previously outlined.

**Key Words:** carcinoma, renal cell; nephrectomy; adrenal glands; treatment outcome; surgical procedures, operative

Robson’s radical nephrectomy, including en bloc resection of the adrenal gland, has been the standard of practice for the treatment of kidney cancer for nearly 40 years. With improved preoperative imaging and earlier detection of many renal tumors the precise indications for adrenalectomy have not been well-defined. In addition, many patients today undergo nephron sparing surgery and the need to remove the ipsilateral adrenal gland in these patients has not been clearly addressed. Urologi-
univariable and multivariable analysis of the risk significance was assessed based on a 2-sided significance level of compared using a log rank test statistic. Statistical significance was estimated using Kaplan-Meier curves and survival and freedom from adrenal recurrence in both was less than 5%. The cumulative probability of overall with Yates’ continuity correction and Fisher’s exact tests normally. The distribution of categorical variables in both dependent samples and Wilcoxon rank sum tests with out adrenalectomy were compared using t tests for 2 independent variables in a Cox proportional hazards model.

RESULTS

Patients undergoing partial nephrectomy and concomitant adrenalectomy were similar to those undergoing partial nephrectomy alone (table 1). Indications for adrenalectomy in 48 patients included 35 adrenal lesions (73%) and 13 upper pole renal tumors with concern for direct invasion into the adrenal gland (27%). Of 35 adrenal lesions treated with concomitant adrenalectomy 80% were indeterminate (26) or suspicious for pheochromocytoma (2) on preoperative triple phase CT or magnetic resonance imaging. There were 7 lesions (20%) suspected to be benign including 6 adenomas and a 10 cm myelolipoma. Renal tumors in the adrenalectomy group were more commonly upper pole (65% vs 31%), high (pT2 or greater) stage (19% vs 6%) and slightly larger (median 3.6 vs 3.0 cm, p = 0.038). Median size of the 13 upper pole renal tumors removed en bloc with adrenal glands was 7.5 cm (range 2.1 to 12). Direct RCC invasion into the adrenal gland occurred in only 1 of 8 patients in whom intraoperative findings confirmed radiographic suspicion of direct adrenal involvement (fig. 1, C), and none of the 5 patients who underwent adrenalectomy based on radiographic suspicion without intraoperative concern for invasion. Of 48 patients undergoing concomitant adrenalectomy 6 (12.5%) experienced any recurrence including adrenal involvement alone (2), other distant metastases (1) and local tumor recurrence in the kidney (3).

The clinical features of patients undergoing concomitant (48) or metachronous (15) adrenalectomy are indicated in table 2. Radiographic tumor size and adrenal gland weight were lesser in the concomitant adrenalectomy group (p = 0.0001). The indication for metachronous adrenalectomy was uniformly a radiographically suspicious lesion in which pathological evidence of metastasis was ultimately present in 11 (73%). Final pathological diagnoses for those patients undergoing concomitant adrenalectomy included normal adrenal gland (18), cortical adenoma (14), cortical hyperplasia (9), myelolipoma (1), pheochromocytoma (2), aldosteronoma (1), direct invasion of the adrenal gland and periadrenal fat by RCC (1), and RCC metastasis (2). Final pathological diagnoses for those undergoing metachronous adrenalectomy included normal adrenal gland (1), cortical adenoma (1), adrenocortical carcinoma (1), pheochromocytoma (1) and metastatic RCC (11).

There was no significant difference in overall survival after partial nephrectomy with or without con-
comitant adrenalectomy (fig. 2). The Kaplan-Meier estimates of overall survival at 5 and 10 years after partial nephrectomy without adrenalectomy were 85.3% (95% CI 83.5–87.0) and 72.4% (95% CI 69.7–75.1), and after partial nephrectomy with adrenalectomy were 82.3% (95% CI 71.0–93.5) and 67.6% (95% CI 49.6–85.6), respectively. Adrenal involvement by RCC was ipsilateral to partial nephrectomy in 12 patients, contralateral in 1 and bilateral in 2. There were 7 patients treated for bilateral adrenal lesions including 3 with von Hippel-Lindau disease with multiple pheochromocytomas, 2 with bilateral adrenal RCC metastases and 2 with no malignancy at adrenalectomy.

During a median followup of 5.5 years (IQR 2.9 to 9.0) RCC recurred in 61 of 1,501 patients with cancer (4.0%) who underwent partial nephrectomy including 11 metachronous adrenal metastases (0.74%), 7 of which were a solitary metastasis. The 11 patients undergo-
ing metachronous adrenalectomy with pathological RCC survived longer than the 4 with concomitant adrenal involvement by RCC. There were 7 patients with metachronous adrenal RCC metastasis (64%) who were alive at a median followup of 7.1 years while all 4 with concomitant adrenal RCC died after surgery at a median of 0.9 years. The Kaplan-Meier estimates of freedom from adrenalectomy for RCC recurrence at 5 and 10 years after partial nephrectomy (without concomitant adrenalectomy) were 99.5% (99.1 to 99.9) and 99.3% (98.9 to 99.8), respectively.

On univariable analysis no specific demographic or clinical tumor characteristic was predictive of the need for adrenalectomy for adrenal involvement by RCC. There were 7 patients with metachronous adrenal RCC metastasis (64%) who were alive at a median followup of 7.1 years while all 4 with concomitant adrenal RCC died after surgery at a median of 0.9 years. The Kaplan-Meier estimates of freedom from adrenalectomy for RCC recurrence at 5 and 10 years after partial nephrectomy (without concomitant adrenalectomy) were 99.5% (99.1 to 99.9) and 99.3% (98.9 to 99.8), respectively.

On univariable analysis no specific demographic or clinical tumor characteristic was predictive of the need for adrenalectomy for adrenal involvement by renal cell carcinoma (table 3). On multivariable analysis larger clinical tumor size was significantly associated with adrenal involvement (p = 0.01). After final pathological examination of partial nephrectomy specimens, several features were associated with adrenal involvement by RCC including larger tumor size (p = 0.004, median 6.0 vs 3.0 cm), advanced pathological stage (p <0.0001, stage T2 or greater in 33% vs 6.1%), higher nuclear grade (p = 0.008, grade 4 in 21% vs 4.4%) and histological subtype (p = 0.01). Renal cancer in all 15 patients with adrenal involvement was of clear cell histology on final pathological analysis.

**DISCUSSION**

In the initial description of the surgical treatment of RCC ipsilateral adrenalectomy was considered part of radical nephrectomy. However, in contemporary practice adrenalectomy is often omitted during laparoscopic and open radical nephrectomy, and the precise indications for adrenalectomy have not been well-defined. In recent surgical series between 35% and 100% of radical nephrectomies have been performed with concomitant adrenalectomy. Some authors continue to recommended adrenalectomy routinely and others would reserve it only for renal tumors larger than 8 cm, or with radiographic evidence of lymphatic or distant metastases. Others have concluded that adrenalectomy should only be omitted for confined renal tumors smaller than 4 cm based on the absence of ipsilateral adrenal metastases in that subgroup. Microscopic adrenal involve-
ment by RCC in the setting of normal radiographic findings is rarely encountered.\(^4,10\) Based on the low incidence of adrenal involvement by RCC some have concluded that adrenalectomy should only be performed for a radiographically suspicious adrenal lesion or if gross disease is present at nephrectomy.\(^11–15\) In this study we found that the only demographic or clinical tumor characteristic predictive of adrenal involvement with renal cancer was renal tumor size (table 3).

Partial nephrectomy was initially described for patients in whom renal failure would develop after radical nephrectomy (solitary kidney with tumor, bilateral tumors) but has subsequently become the gold standard for small (less than 4 cm, T1a) tumors amenable to such an approach with some expanding the indications to larger tumors (4 to 7 cm, T1b).\(^16–19\) Nevertheless, partial nephrectomy remains greatly underused in this country with fewer than 10% of renal tumors managed using a nephron sparing approach in the Surveillance, Epidemiology, and End Results registry.\(^20\) Cancer specific outcomes are comparable and overall survival is superior when comparing similar groups of patients undergoing partial or radical nephrectomy.\(^16–19\) With an aging population highly susceptible to hypertension, diabetes and dyslipidemia, renal preservation has become a major focus in kidney cancer management. In addition, since many patients with localized RCC have an excellent long-term survival it is becoming even more important to examine the effect of interventions such as adrenalectomy on the overall morbidity and mortality of kidney cancer. There have been no published reports to our knowledge specifically describing adrenal management during partial nephrectomy nor is there consensus regarding the indications for adrenalectomy during partial nephrectomy. The traditional teaching is to remove the adrenal gland during partial nephrectomy performed for any upper pole tumor. At our institution we have generally reserved adrenalectomy for radiographically suspicious lesions and when the removal of the renal tumor would not be feasible.

![Kaplan-Meier curve showing overall survival in patients undergoing partial nephrectomy with or without adrenalectomy (Ax)](image)

**Figure 2.** Kaplan-Meier curve showing overall survival in patients undergoing partial nephrectomy with or without adrenalectomy (Ax)

**Table 3.** Cox proportional hazards model of factors predicting time to adrenalectomy for RCC recurrence

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariable</th>
<th>Cox Proportional Hazards Model</th>
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<tr>
<td></td>
<td>Estimate (approximate 95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Estimate (approximate 95% CI)</td>
</tr>
<tr>
<td>Age</td>
<td>−0.002 (−0.040–0.041)</td>
<td>0.91</td>
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<tr>
<td>Gender (male)</td>
<td>0.570 (−0.080–1.499)</td>
<td>0.09</td>
</tr>
<tr>
<td>Renal tumor size (cm)</td>
<td>0.100 (−0.041–0.172)</td>
<td>0.14</td>
</tr>
<tr>
<td>Renal tumor side (rl)</td>
<td>0.499 (−0.092–1.243)</td>
<td>0.11</td>
</tr>
<tr>
<td>Renal tumor location (upper)</td>
<td>0.482 (−0.047–1.038)</td>
<td>0.07</td>
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without en bloc resection of the adrenal gland. Since partial nephrectomy is being increasingly recommended for the management of renal masses smaller than 7 cm we investigated the impact of our current management schema on adrenal recurrence and survival.

The incidence of adrenal involvement by RCC at radical nephrectomy has been reported to be between 2% and 8%. Direct invasion of the adrenal gland by RCC confers a poor prognosis, which has been increased from stage T3a to T4 in the most recent TNM staging system. Adrenal metastases can be ipsilateral or contralateral to the renal cancer, and have been detected up to 38 years after nephrectomy. Resection of adrenal or pulmonary metastasis is frequently recommended since metastasectomy improves outcomes in selected patients. Patients with isolated adrenal metastasis have better outcomes than those with adrenal plus other metastases, especially if the duration between nephrectomy and adrenal metastasis is greater than 18 months. Thus, the literature continues to support adrenalectomy for solitary adrenal metastasis at the time of detection (synchronous or metachronous).

Only indeterminate adrenal lesions suspected to be metastatic RCC or primary adrenal neoplasms (pheochromocytoma, adrenocortical carcinoma) should be removed on the basis of radiographic suspicion. Radiographic findings consistent with adrenal adenoma or myelolipoma are sufficient to omit adrenalectomy, although some clinicians might consider evaluating incidental lesions for subclinical biochemical function. At the minimum preoperative screening for pheochromocytoma should be performed for all adrenal lesions. Using these relatively stringent clinical criteria we found that a surprisingly high rate of benign disease was present even during adrenalectomy for cause in our series (87%) and that only 3 patients had adrenal involvement with RCC.

When considering the removal of the ipsilateral adrenal gland in the presence of large and/or upper pole renal tumors our data confirm the safe omission of adrenalectomy in more than 90% of patients with upper pole renal tumors. Direct RCC invasion into the adrenal gland occurred in only 1 of 8 patients with intraoperative suspicion and none of the 5 patients who underwent adrenalectomy based on radiographic suspicion alone. We conclude that the adrenal gland should only be removed if intraoperative findings confirm that the renal tumor is densely adherent or invades the adrenal gland. In such cases radical nephrectomy may also be considered when the contralateral kidney is normal. Therefore, we recommend consenting patients for the possibility of adrenalectomy and/or radical nephrectomy if there is radiographic suspicion of direct adrenal involvement, but reserving adrenalectomy for tumors with gross invasion of the adrenal gland at surgery.

Our data indicate that preserving the adrenal gland does not increase the death rate after OPN. The incidence of adrenalectomy for RCC metastasis after partial nephrectomy is surprisingly low in this series (0.74%). Only 15 patients underwent adrenalectomy for a radiographic lesion suspicious for RCC metastasis after undergoing partial nephrectomy. Of these 15 cases 11 were pathologically confirmed RCC metastases. Although the majority of adrenal lesions resected metachronously contained metastatic RCC, there was no demonstrable penalty to later resection as only 2 patients died of kidney cancer. In fact only 1 of 2,017 patients (0.049%) experienced a solitary metastasis to the adrenal and died of cancer. In summary, these data indicate a truly minute oncological benefit to routine adrenalectomy in this population and certainly no measurable penalty for adrenal preservation during partial nephrectomy.

Lastly adrenalectomy is not without surgical and medical morbidity. During surgery adrenal venous bleeding can be troublesome and necessitate blood transfusion. Moreover some patients with kidney cancer, especially those with von Hippel-Lindau disease, are at significant risk for bilateral adrenal lesions. Adrenal insufficiency (Addison's disease) occurs in as many as 20% of patients treated with adrenalectomy for Cushing's disease, the incidence of which increases with time. While uncommon after unilateral adrenalectomy with a contralateral gland presumed to be normal, Addison's disease was first reported after nephrectomy with adrenalectomy almost 60 years ago. Such patients can experience Addisonian crisis, and require replacement with glucocorticoids and mineralocorticoids. More recent clinical data indicate that unilateral adrenalectomy is associated with some impairment in adrenocortical function as assessed by an adrenocorticotropic hormone stimulation test. Therefore, unilateral adrenalectomy may not be without some deleterious effects, although we found no negative impact on overall survival.

CONCLUSIONS

Adrenalectomy can be safely omitted for the majority of patients with renal tumors amenable to neophron sparing surgery as the majority will not experience adrenal metastasis during followup. Only when an adrenal lesion is indeterminate (ie not clearly defined as an adenoma or myelolipoma by dedicated cross-sectional imaging) or intraoperative
findings suggest that removal of the renal tumor would not be feasible without en bloc resection of the gland should adrenalectomy be performed during partial nephrectomy.

ACKNOWLEDGMENTS
Wei Liao and Mary Federico provided database assistance. Erick Remer assisted in CT image preparation.

REFERENCES

EDITORIAL COMMENT
Radical nephrectomy has typically included adrenalectomy as part of the operation. Given the diagnosis of increasing numbers of small renal tumors and the advent of laparoscopic surgery with partial nephrectomy, management of the adrenal gland has changed. Under these new circumstances the adre-
nal gland is frequently preserved. Is it appropriate to preserve the adrenal gland with smaller tumors? The authors address a large number of cases. Unless there is an adrenal mass radiologically or suspicion of direct invasion it would appear that adrenalectomy is not necessary. Even in higher risk situations the relative risk of carcinoma involving the adrenal gland remains low.

Excision of the adrenal gland should be distinguished from excision of perinephric tissue over a renal mass because there is a significant incidence of capsular invasion or even perinephric fat involvement with small renal masses compared to any involvement of the adrenal gland. Partial adrenalectomy with a frozen section is another potential option in cases in which there is suspicion of tumor within the adrenal gland. Management with partial adrenalectomy with potential bleeding may be more complicated but nonetheless can be considered. Sacrificing adrenal tissue unnecessarily can theoretically create problems in the future, particularly if there were excision of the adrenal with a contralateral renal tumor. A patient without any adrenal tissue presents a difficult clinical management problem. In summary, preservation of the adrenal gland appears reasonable with almost all partial nephrectomies.

Fray F. Marshall
Department of Urology
Emory University School of Medicine
Atlanta, Georgia