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ROUTINE ADRENALECTOMY IS UNNECESSARY DURING SURGERY FOR LARGE AND/OR UPPER POLE RENAL TUMORS WHEN THE ADRENAL IS RADIOGRAPHICALLY NORMAL

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Abstract

INTRODUCTION AND OBJECTIVES—Concurrent adrenalectomy during renal surgery for RCC was once routine. More recent data suggest that adrenalectomy should be reserved for tumors ≥ 7 cm, particularly those involving the upper pole. We evaluated the radiographic and pathologic incidence of adrenal involvement in patients undergoing renal surgery for RCC ≥ 7 cm.

METHODS—Patients undergoing renal surgery for tumors ≥ 7 cm between 1999 and 2008 were identified from our kidney cancer registry. Fisher's exact test was used to determine whether radiographic tumor location predicted adrenal involvement. Kaplan-Meier method and Cox proportional hazard regression models were used to analyze the impact of adrenal resection on outcome.

RESULTS—Of 1,650 patients, we identified 179 patients who underwent surgery for RCC ≥ 7 cm. Of these 91 underwent concurrent total ipsilateral adrenalectomy at the time of renal surgery with pathological adrenal involvement confirmed in 4.4% (4/91). Upper pole location did not predict involvement ($p=0.83$). Preoperative adrenal imaging was 100% sensitive and 92% specific for detection of adrenal involvement by RCC with a 100% NPV. No survival advantage was noted on multivariable analysis comparing those who underwent adrenal resection to the cohort ($n=88$) whose adrenal was spared ($p=0.38$).

CONCLUSIONS—Synchronous ipsilateral adrenal involvement with RCC is rare, even in cases of large and/or upper pole tumors making routine adrenalectomy unnecessary. Pre-operative adrenal imaging is highly sensitive and should inform the decision regarding adrenalectomy more than tumor size or location.

Keywords

renal cell carcinoma; adrenal; upper pole

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Supplementary Material can be found at the following URL:

<http://www.fccc.edu/docs/healthProfessionals/KutikovSupplementaryMaterial01.pdf>

INTRODUCTION

Surgery remains the primary modality in the treatment of RCC. RN has long been held as the standard for surgical cure of localized disease. In the 1960s, Robson described RN to include early ligation of the renal vessels and removal of the entire kidney, all accompanying perirenal fat, Gerota's fascia, regional lymph nodes and the adrenal gland.¹ These precepts guided exenterative surgery for RCC for the ensuing two decades. As surgical experience grew and outcomes were analyzed, the tenets of "wide excision" of stage I cancer bearing organs (including the kidney) have been challenged. It is now well recognized that 5 year CSS rates for NSS match those for RN and are in excess of 90% for most T1 RCCs.²

Concurrent with the excellent results achieved by NSS has been the development of renal MIS, most notably LRN. Initial concerns with LRN, including a higher potential risk of systemic and/or local recurrence, have not been realized.² These concerns initially arose due to the less "radical" approach perceived with LRN, which often omits lymph node sampling and adrenalectomy. Collective data from both the NSS and LRN experience have now called the value of routine adrenalectomy into question.^{3, 4}

Nonetheless, current practice standards support the role of adrenalectomy during surgery for large RCCs.⁴⁻⁶ Recently suggested guidelines advocate for adrenalectomy in patients with tumors ≥ 7 cm that are in the upper pole.⁴ Here we evaluate the incidence and predictors of adrenal involvement in patients undergoing renal surgery for RCC ≥ 7 cm at our center.

METHODS

We retrospectively reviewed our prospectively-maintained IRB approved Fox Chase Cancer Center kidney cancer registry. Patients undergoing renal surgery between 1999 and 2008 for tumors ≥ 7 cm were identified.

Clinical, pathological, demographic, pre-operative imaging, management of the adrenal at surgery, and post-operative outcomes were all analyzed. Surgical procedures were performed by different surgeons using standardized techniques for open, laparoscopic, and robot-assisted RN and NSS. Decision regarding whether to resect the adrenal was based on judgment of each clinician. RCC stage was assigned according to the AJCC 2002 TNM Classification. Tumor grade for ccRCC was determined using the Fuhrman grading system. For the purposes of statistical analysis, tumors with grade I and II were considered low grade, while Grade III and IV tumors were classified as high grade. Tumors with chromophobe histology or type I papillary tumors were considered low grade, while type II papillary or sarcomatoid RCC were coded as high grade.

Tumor histology was assigned according to the 2004 WHO criteria. Any radiographic abnormality of the adrenal including enlargement, nodularity or presence of a mass was deemed abnormal.

Surgical follow-up consisted of a physician visits and radiographic surveillance at regular intervals. Duration of follow up was the latest information available on file until the date of death. Cause of death was confirmed with death certificates.

In patients who underwent adrenal resection at the time of surgery, Fisher's exact test was employed to determine whether tumor location predicted adrenal involvement. OS was estimated for patients who did and did not undergo adrenalectomy using the Kaplan-Meier method and was compared with the log-rank test. Cox proportional hazard regression models were used to analyze the impact of adrenal resection on outcomes. All tests were

two-sided with a p value ≤ 0.05 considered significant. Statistical analyses were conducted using STATA version 10.1 for Windows (StataCorp, College Station, TX).

RESULTS

We identified 1,650 patients who underwent surgery for an enhancing renal mass between 1999 and 2008 in our kidney cancer database. All patients in the cohort contained data regarding renal tumor size and management of the adrenal at the time of resection. After excluding those without RCC, we identified 179 patients who underwent surgery for RCC ≥ 7 cm. This included 88 patients in a control cohort who did not undergo adrenalectomy at surgery and 91 who underwent concurrent ipsilateral total adrenalectomy at the time of their renal surgery. All but one patient in the latter cohort underwent RN, whereas the majority of the partials for large RCC were associated with adrenal preservation (Table 1).

Adrenal radiographic abnormalities were seen in a minority (13% (12/91)) of patients in whom the adrenal was resected (Table 2). The incidence of pathologically confirmed adrenal involvement by RCC was 4.4% (4/91) of the overall cohort and 33% (4/12) of patients with radiographic abnormalities of the adrenal gland. Importantly, 3 of the 4 in whom the adrenal was pathologically involved had N+ and/or M+ disease. All cases of pathological RCC involvement were identified correctly on preoperative imaging. The PPV for pre-operative imaging was 33.3% (4 of 12 patients), while the NPV was 100% (79 of 79 patients), meaning there were no cases where the adrenal was radiographically normal but involved by RCC. The sensitivity and specificity for detection of adrenal involvement on pre-operative imaging were 100% (4 of 4 patients) and 90.1% (79 of 87 patients), respectively.

Overall, 46 patients (50.5%) were definitively identified as having an upper pole tumor on pre-operative imaging, while 30 patients (33.0%) had either an interpolar or a lower pole lesion. Definitive polar location was unassignable in 15 patients (16.5%). Three of 46 (6.5%) resected adrenal glands associated with upper pole tumors were involved by RCC, while 1 of 45 (2.2%) non-upper pole tumors was associated with adrenal involvement. As such, upper pole location did not predict pathological adrenal involvement ($p=0.83$) when patients with unassignable polar location ($n=15$) were excluded from the analysis. Even if these 15 patients were included in the analysis and assumed to have had non-upper pole tumors, tumor location was not associated with adrenal involvement by RCC ($p=0.62$).

The group of patients in whom adrenal resection was omitted differed with those patients who had their adrenal removed with respect to surgical modality ($p<0.0001$), tumor histology ($p=0.01$), and grade ($p=0.001$) (Table 1). After a median follow-up of 11.9 months (mean 20.11, range 0–90.2 months) no new adrenal lesions — ipsilateral nor contralateral — were documented in patients whose adrenal was spared.

At a median postoperative follow-up of 15 months (range 0–111), 64 patients had died, including 42/91 who had adrenalectomy and 22/88 who did not. Estimated median postoperative OS in all patients was 42 months. The estimated median OS in patients with nodal or distant disease (N+ and/or M+) who had adrenalectomy was 21 months versus 34 months for patients with nodal or distant disease whose adrenal was spared ($p=0.9$) (Figure 1A). No statistically significant OS difference was noted between patients with and without adrenalectomy and localized disease ($p=0.2$) (Figure 1B).

In a multivariable analysis controlling for presence of distant disease, sex, surgical modality, histology, grade, tumor size, and age at surgery, status of adrenal resection at the time of nephrectomy had no statistical influence on patient OS (HR 0.75; 95% CI 0.40, 1.43; $p=0.38$). In this analysis absence of metastases (HR 0.43; 95% CI 0.24, 0.77; $p=0.005$), non-clear cell histology (HR 0.192; 95% CI 0.05, 0.78; $p=0.02$) was associated with an increased

OS while high grade disease (HR 3.59; 95% CI 1.59, 8.09; $p=0.001$) was associated with decreased OS.

DISCUSSION

Removal of the ipsilateral adrenal has long been cited as an essential part of RN. Historically the two entities were so closely linked that in early descriptions RCC was termed “hypernephroma” due to its histological resemblance of the adrenal gland.⁷ More recently the necessity of adrenalectomy at the time of nephrectomy has been challenged.⁷⁻⁹ In a recent review, O'Malley and colleagues analyzed the available data regarding the necessity of adrenalectomy at the time of renal surgery.⁴ The authors proposed a management strategy suggesting that the adrenal should be spared in most instances.⁴ The three exceptions to their recommendation include cases when: (1) imaging indicates a definitive or “equivocal” adrenal abnormality, (2) tumor thrombus extends to or above the level of the adrenal vein and (3) the renal tumor is ≥ 7 cm in size and in the upper pole. Unfortunately these recommendations are based largely on low level evidence,^{5, 6} as the authors concede.⁴ In fact, to our knowledge, no study prior to this has specifically examined a cohort of patients with large upper pole renal tumors to assess whether adrenal resection is warranted.

Routine resection of healthy adrenal glands exposes the patient to small but unjustified intraoperative risks.³ Furthermore, adrenalectomy may give rise to challenging clinical circumstances where patients may be subject to life-long adrenal insufficiency – a condition that significantly impacts quality of life^{10, 11} and possibly life-expectancy.¹² While the rarity of such scenarios has undoubtedly helped motivate “routine” adrenalectomy for RCC, evidence-based strategies must replace “unlikely to be a problem” mantra. As such, we examined the validity of long-standing urologic dogma that the ipsilateral adrenal gland of patients with large and/or upper pole renal tumors must be routinely resected.⁴⁻⁶

Of the 1650 patients in our prospectively-maintained dataset, 91 underwent adrenal resection at the time of renal surgery for tumors ≥ 7 cm. Of these patients, 4.4% ($n=4$) had evidence of adrenal involvement by RCC. In patients with localized disease ($n=57$), only one (1.8%) had adrenal involvement by RCC upon resection. Such low incidence of adrenal involvement in our cohort of large tumors is consistent with the rates of $\sim 1\%$ to $\sim 5\%$ reported in series that include renal masses of all sizes.^{4, 8, 13-18} Indeed, conflicting data exist regarding whether size alone – independent of the tumor's ability to invade perinephric tissues or renal vein – is a predictor of adrenal involvement by RCC.^{4, 19, 20}

In this group of clinical T2+ patients who had adrenal resection at the time of nephrectomy, OS after a median follow-up of 20.2 months was 75.9% (69 of 91). We compared these outcomes to a cohort of cT2+ patients who underwent renal surgery for tumors ≥ 7 cm, but had the ipsilateral adrenal left in place ($n=88$). No statistically significant survival advantage to adrenalectomy was noted when patients with distant and locally recurrent RCC were compared in the two cohorts (Figures 1A and 1B). Because the two cohorts differed significantly in clinicopathological variables (Table 1), a multivariable analysis was performed. Controlling for presence of distant disease, gender, surgical modality, histology, grade, tumor size, and age at surgery, no effect of adrenal resection on OS was noted. Although these findings are limited by relatively small sample size, they are consistent with reports of others who have documented a lack of a survival advantage to ipsilateral adrenalectomy for cohorts with heterogeneous and smaller renal tumor sizes.^{3, 4, 14, 18} Furthermore, Lane and colleague recently presented evidence that there is no “penalty” for adrenal preservation, as patients in their series who underwent delayed adrenal metastases resection ($n=11$) fared no worse than those who had the adrenal resected at the time of renal

surgery.³ After a mean follow-up of 21.2 months, no adrenal recurrences were documented in our group of patients whose adrenal was spared.

Of the 91 patients with large renal tumors who had the ipsilateral adrenal resected at the time of renal surgery, 50.5% had renal tumors in the upper pole of the renal unit. Despite the fact that all tumors in our cohort were at least 7 cm in size, upper pole location did not predict adrenal involvement ($p=0.83$). These data are consistent with reports from published cohorts with heterogeneous renal tumor sizes^{3, 19, 21–23} and suggest that the current standard to resect all ipsilateral adrenal glands in patients with large upper pole renal tumors is likely unjustified^{4–6}. Indeed, the data upon which the recommendation for routine adrenalectomy for upper pole tumors has been made are at best inconclusive, suggesting that this recommendation is based more on the possible than the probable.^{4, 7, 8, 13, 15, 20, 24–26}

The majority of these manuscripts make subjective conclusions in their discussion, advocating the potential use of routine adrenalectomy for large upper pole renal tumors, perhaps in an effort to not overstate their call to spare most adrenals. In fact, only two publications contain data that allow for a statistical analysis of a relationship between upper pole location and adrenal involvement (Supplementary Material).^{7, 25} To be sure, the manuscripts that contain most robust data regarding adrenalectomy objectively demonstrate no statistical correlation between upper pole tumor location and adrenal involvement.^{3, 19}

In our series, all cancerous adrenals were identified as suspicious on pre-operative scans. Indeed 100% sensitivity and 100% NPV of modern imaging for detection of RCC adrenal metastases has been described by other investigators.^{25, 27, 28} The excellent performance of cross-sectional radiography of the adrenal has been confirmed prospectively by at least one group.¹⁷ While some authors have reported rare adrenal lesions that are missed by pre-operative imaging,^{8, 13, 20} it appears inaccurate radiological interpretation is to blame.²² Of note, it has been suggested that when in the setting of RCC an adrenal gland cannot be appropriately visualized on pre-operative imaging, the gland should be presumed infiltrated by the renal mass and removed.^{4, 27} More recently, Lane and colleagues suggested that intraoperative assessment of adrenal adherence/invasion by the renal tumor is reliable and could be used to guide final decisions regarding adrenal resection in cases where pre-operative imaging indicates direct adrenal invasion by the tumor.³

In our series eight patients were noted to have a radiographic abnormality in the ipsilateral adrenal only to reveal normal adrenal tissue on final pathology. As such, the PPV of imaging in our cohort was 33.3% and specificity was calculated at 90.1%. Although a handful of investigators have reported more impressive PPV's^{8, 20}, our data are consistent with reports from other centers in patients with smaller tumors^{3, 13, 17, 25, 27, 28} and demonstrate the rigor with which we looked for any radiographic adrenal abnormality. 62.5% (5 of 8) false positive results in our cohort were due to radiographic suspicion of direct tumor invasion into the adrenal rather than an adrenal mass. Certainly, some upper pole renal tumors directly invade the adrenal, and although this is a described mechanism of RCC spread, it appears to be rare.³ As such, AJCC now stages this clinical scenario as pT4, while the more common metastatic spread is now considered M1.

The specificity of adrenal imaging in the setting of an enhancing renal mass likely can be improved if tenants of modern adrenal radiography are closely followed.²⁹ Adrenal nodules with imaging characteristics inconsistent with adenoma should be suspected of representing RCC metastases.³⁰ Resection of isolated adrenal metastases – an extremely rare scenario – currently represents the standard of care, since significant long-term survival has been demonstrated in these cohorts.⁴³ If imaging characteristics of an ipsilateral adrenal lesion are consistent with a small (<4 cm) adenoma, we believe resection can be safely omitted, as long as the adenoma is proven metabolically inactive on pre-operative testing.

CONCLUSION

These data demonstrate that synchronous ipsilateral involvement of the adrenal by RCC is extremely rare even in patients with large (≥ 7 cm) and/or upper pole renal tumors. Routine adrenalectomy even in patients with large and/or upper pole renal tumors does not appear to be required. Furthermore, we confirm that modern radiographic imaging is extremely sensitive in the detection of adrenal pathology, and should guide management decisions regarding the necessity for concurrent adrenalectomy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Comparison of overall survival for patients undergoing renal surgery with and without adrenal resection, stratified by (A) patients with distant disease (N+ and/or M+) and (B) patients with localized disease.

TABLE 1

Clinicopathological demographics of patients who underwent renal surgery for renal tumors ≥ 7 cm divided into 2 cohorts – those in whom the adrenal gland was removed at the time of the renal surgery and those in whom it was preserved.

Variable	Tumors ≥ 7 cm Concomitant Adrenalectomy	Tumors ≥ 7 cm without Concomitant Adrenalectomy	p value
Total patients	91	88	
Gender			0.1
Male (%)	69 (75.8)	56 (63.6)	
Female (%)	22 (24.2)	32 (36.4)	
Median Tumor Size in cm (range)	9.5 (7–24)	8.5 (7–25)	0.07
RCC histologic subtype			0.01
Clear Cell (%)	80 (87.9)	47 (53.4)	
Papillary (%)	3 (3.3)	19 (21.6)	
Sarcomatoid (%)	7 (7.7)	7 (8.0)	
Chromophobe (%)	1 (1.1)	10 (11.4)	
Collecting Duct (%)	0	1 (1.1)	
Other (%)	0	4 (4.5)	
Grade			0.001
High(%)	68(75.6)	41 (46.6)	
Low(%)	22 (22.4)	40 (45.5)	
Unknown(%)	1 (1.1)	7 (8.0)	
Primary tumor stage			0.04
T2 (%)	36 (39.6)	52 (59.1)	
T3a (%)	28 (30.7)	18 (20.5)	
T3b (%)	26 (28.6)	16 (18.1)	
T4 (%)	1 (1.1)	2 (2.3)	
Node Status			0.45
N0/Nx (%)	74 (81.3)	77 (87.5)	
N1 (%)	6 (6.6)	5 (5.7)	
N2 (%)	11 (12.1)	6 (6.8)	
Metastatic Disease Status			0.16
Mx/M0 (%)	65 (71.4)	71 (80.7)	
M1 (%)	26 (28.6)	17 (19.3)	
Distant disease (N+ or M+) (%)	34 (37.3)	22(22.7)	0.07
Surgical Procedure			<0.0001 (radical vs partial)
Radical Nephrectomy (%)	90 (98.9)	65 (74)	
Open	64	34	

Variable	Tumors ≥ 7 cm Concomitant Adrenalectomy	Tumors ≥ 7 cm without Concomitant Adrenalectomy	p value
<i>Laparoscopic</i>	26	30	
<i>Robotic</i>	0	1	
Partial Nephrectomy (%)	1 (1.1)	23 (26)	
<i>Open</i>	0	19	
<i>Laparoscopic</i>	1	1	
<i>Robotic</i>	0	3	
Age at Surgery	62(37–89)	61 (21–90)	0.5
Follow-up (months)	Mean 26.6 Median 20.2 Range 0.3–110.6	Mean 20.1 Median 11.9 Range 0.0–90.2	0.02

TABLE 2

Characteristics of patients with ipsilateral adrenal preoperative imaging abnormality in whom the adrenal gland was radiographically abnormal and the adrenal was removed at the time of renal surgery. Of note 3 of 4 in whom the adrenal was radiographically abnormal and pathologically involved had N+ and/or M+ RCC.

	Age (yrs)	Sex	Tumor Size (cm)	Side	Thrombus Level	Pathologic Stage	Histology	Grade	Upper Pole Location	Pre-operative imaging	Pathologic Findings in Adrenal Gland
1	48	M	24	R	None	T3a N0M1	Clear Cell	IV	Y	Tumor extension into R adrenal	RCC present
2	51	F	12	L	None	T2N1M1	Sarcomatoid	High	N	Adrenal nodule	RCC present
3	78	F	11.5	L	II	T3b NxM0	Clear Cell	II	Y	L adrenal nodule	RCC present
4	58	M	7	R	I	T3b N2M0	Clear Cell	II	Y	2.7 cm adrenal mass	RCC present
5	77	M	11.5	L	None	T2N0M0	Clear Cell	III	N	Tumor extension into L adrenal	Normal adrenal
6	49	M	17	R	None	T2N0M0	Clear Cell	III	N/A	Bilateral adrenal enlargement R>L	adrenal cortical hyperplasia
7	57	M	10	R	None	T2NxM0	Clear Cell	II	Y	2cm R adrenal mass	adrenal cortical hyperplasia
8	55	M	11.5	R	None	T2N0M0	Clear Cell	II	Y	Tumor extension into R adrenal	Normal adrenal
9	65	M	17	L	None	T3a N0M0	Clear Cell	III	Y	Tumor extension into L adrenal	adrenal cortical hyperplasia
10	60	M	8.5	L	I	T3b N0M0	Clear Cell	IV	Y	Likely adrenal metastasis	Normal adrenal
11	49	M	17.5	L	I	T3b N0M0	Clear Cell	III	Y	Tumor extension into L adrenal	Normal adrenal
12	64	M	10	R	II	T3b N0M1	Clear Cell	IV	Y	Tumor extension into R adrenal	Normal adrenal