



Platinum Priority – Kidney Cancer

Editorial by Christian G. Stief on pp. 465–466 of this issue

Routine Adrenalectomy in Patients with Locally Advanced Renal Cell Cancer Does Not Offer Oncologic Benefit and Places a Significant Portion of Patients at Risk for an Asynchronous Metastasis in a Solitary Adrenal Gland

Christopher J. Weight^a, Simon P. Kim^a, Christine M. Lohse^b, John C. Cheville^c,
R. Houston Thompson^a, Stephen A. Boorjian^a, Bradley C. Leibovich^{a,*}

^a Department of Urology, Mayo Clinic, Rochester, MN, USA

^b Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

^c Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

Article info

Article history:

Accepted April 7, 2011
Published online ahead of
print on April 16, 2011

Keywords:

Survival
Radical nephrectomy
Adrenalectomy
Renal cell cancer
Partial nephrectomy

Abstract

Background: The indications for the removal of the ipsilateral adrenal gland in patients with renal cell carcinoma (RCC) and the long-term outcomes have not been well studied.

Objective: We evaluated the risk of synchronous and asynchronous adrenal involvement in patients with RCC and the effect of adrenalectomy on recurrence and survival in a large, single-institution cohort.

Design, setting, and participants: From 1970 to 2006, 4018 consecutive patients with RCC treated by surgical extirpation (radical nephrectomy [RN]: 3107; partial nephrectomy [PN]: 911) from Mayo Clinic were studied for adrenal involvement. Risk of asynchronous adrenal metastasis and cancer-specific survival (CSS) were also compared between those who underwent concomitant ipsilateral adrenalectomy ($n = 1541$) and those who did not ($n = 2477$) using multivariate Cox models.

Intervention: Surgical removal of the adrenal gland at the time of kidney tumor resection.

Measurements: Primary outcome is cancer specific survival; secondary outcomes are incidence of synchronous and asynchronous adrenal metastases.

Results and limitations: Median postoperative follow-up among those still alive was 8.2 yr (interquartile range [IQR]: 5.3–13.6). Synchronous ipsilateral adrenal involvement was rare ($n = 88$; 2.2%). Ipsilateral adrenalectomy at the time of nephrectomy did not lower the risk of subsequent adrenal metastasis (hazard ratio [HR]: 0.96; 95% confidence interval [CI], 0.64–1.42) or improve CSS (HR: 1.08; 95% CI, 0.95–1.22). The development of asynchronous adrenal metastasis occurred in 147 patients (3.7%) at a median of 3.7 yr (IQR: 1.2–7.7) after initial surgery. The risk of developing an ipsilateral versus a contralateral asynchronous adrenal metastasis was equivalent at 10 yr in those who did not undergo adrenalectomy at initial surgery. This study is limited by its single-institution, nonrandomized nature.

Conclusions: Routine ipsilateral adrenalectomy in patients with high-risk features does not appear to offer any oncologic benefit while placing a significant portion of patients at risk for metastasis in a solitary adrenal gland. Therefore, adrenalectomy should only be performed with radiographic or intraoperative evidence of adrenal involvement.

© 2011 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Department of Urology, RO_GO_07_130URL, 201 West Center Street, Mayo Clinic, Rochester, MN 55905, USA. Tel. +1 507 774 3982.

E-mail address: Leibovich.bradley@mayo.edu (B.C. Leibovich).

1. Introduction

During the time Robson described the radical nephrectomy (RN), including routine ipsilateral adrenalectomy [1], preoperative imaging was marginal, and the average presenting tumor was large, symptomatic, and often locally invasive, mandating aggressive surgery. Subsequent research rooted in this logic found that this aggressive approach was “superior” in terms of oncologic control when compared to a simple nephrectomy, but these differences were not significant [2]. A few years later, the incidence of ipsilateral adrenal involvement was described as 10% in a sample of 58 patients, and this percentage has, in some minds, become urologic dogma [3]. These limited data suggesting improved outcomes with radical surgery combined with the relative ease of removal laid the foundation for routine ipsilateral adrenalectomy [4].

However, perfunctory use of computed tomography (CT) imaging has decreased the stage at which the average patient presents with renal cell carcinoma (RCC). Now, the majority of renal tumors are small (<7 cm) and asymptomatic [5,6]. This stage migration has necessitated a reevaluation of the role of radical surgery, bringing to the forefront discussions of partial nephrectomy (PN) and the sparing of the ipsilateral adrenal gland [7,8]. Recent data support a low incidence of adrenal involvement, with most contemporary series reporting frequencies <5% [9] and, in cases of PN, <1% [7]. Imaging improvements have allowed clinicians to rest comfortably in the knowledge that a negative adrenal gland on CT will be uninvolved when evaluated pathologically, with a negative predictive value of 98% when data from 8 studies totaling 2443 are combined [8,10–15].

Despite many publications calling for an end to routine adrenalectomy [7,8,16], many continue to advocate it in subsets of patients even with negative preoperative imaging [9,17–19]. However, most studies to date have focused on the incidence of adrenal involvement at the time of surgery, and relatively few have studied the incidence of asynchronous adrenal involvement (both ipsilateral and contralateral) or long-term cancer specific survival (CSS). We therefore evaluated these factors in a large, single-institution cohort.

2. Methods

2.1. Patient selection

After obtaining institutional review board approval and using the Mayo Clinic Nephrectomy Registry, we identified 4018 patients treated with RN or PN for unilateral, sporadic, RCC between 1970 and 2006. The indications evolved for ipsilateral synchronous adrenalectomy from a historical RN in the early part of the cohort to the current practice of removing the adrenal gland only in cases when preoperative imaging demonstrated adrenal involvement or there was intraoperative concern for adrenal involvement. The contralateral adrenal gland was only removed with preoperative or intraoperative evidence of an adrenal lesion. Patients were considered to have synchronous ipsilateral adrenal involvement in cases of noncontiguous ipsilateral adrenal metastases and contiguous extension of RCC into the ipsilateral adrenal gland. We

separated pT4 tumors into those that were classified as pT4 because of invasion beyond Gerota’s fascia and those that were classified as pT4 because of contiguous extension into the ipsilateral adrenal gland. A *locally advanced tumor* was defined as an M0 tumor that was pN1 or pT3a, pT3b, pT3c, or pT4. A urologic pathologist (JCC) reviewed the microscopic slides from all tumor specimens for the pathologic features of interest. Disease status and vital status for patients in the nephrectomy registry are updated yearly.

2.2. Statistical methods

Comparisons of clinical, surgical, and pathologic features among patient groups were evaluated using Wilcoxon rank sum and χ^2 tests. CSS and survival free of asynchronous adrenal metastases were estimated using the Kaplan-Meier method. Univariate and multivariable associations with death from RCC and asynchronous adrenal metastases were evaluated using Cox proportional hazards regression models. Univariate and multivariable associations with synchronous adrenal involvement or metastases were evaluated using logistic regression models. Multivariable models were developed using a stepwise selection procedure, with the *p* value for a feature to enter or leave the model set to 0.05. Statistical analyses were performed using the SAS statistical software package (SAS Institute, Cary, NC, USA). All tests were two-sided, and *p* values <0.05 were considered statistically significant.

3. Results

3.1. Associations with ipsilateral adrenalectomy

Clinical, surgical, and pathologic features for the 4018 patients studied are summarized in Table 1.

3.2. Incidence and associations with synchronous adrenal involvement or metastases

There were 95 patients (2.4%) with synchronous adrenal involvement. Of those, 81 had ipsilateral adrenal involvement only (41 with ipsilateral metastasis and 40 with direct invasion), 7 had synchronous contralateral adrenal metastases only, and 7 had both synchronous ipsilateral adrenal involvement and synchronous contralateral adrenal metastases. Multivariable associations with synchronous adrenal involvement or metastases are summarized in Table 2.

The incidence of synchronous ipsilateral adrenal involvement, when patients were stratified by various high-risk features, was as follows: upper pole in 3.4% patients (42 of 1229) versus other locations in 1.6% (46 of 2789); tumor size >7 cm in 5.0% of patients (74 of 1467) versus tumor size ≤7 cm in 0.5% (13 of 2513); tumor thrombus in 7.3% of patients (54 of 735) versus no tumor thrombus in 1.0% (34 of 3283); and metastatic RCC in 14.6% of patients (72 of 493) versus locally advanced, nonmetastatic RCC in 1.9% (16 of 839).

Of the 88 patients with synchronous ipsilateral adrenal involvement, only 33 had preoperative imaging and operative notes available for review at the time of writing. Thirty-two patients (97%) had preoperative scans for adrenal involvement, including 8 where the adrenal gland was not visualized and 24 where nodular masses were identified within the adrenal gland. One patient had negative imaging

Table 1 – Comparison of clinical, surgical, and pathologic features by ipsilateral adrenalectomy for 4018 patients

Feature	Ipsilateral adrenalectomy		p value
	No (n = 2477)	Yes (n = 1541)	
Age at surgery, yr	Mean (median; range) 61.9 (63; 19–91)	62.6 (64; 19–92)	0.17
Tumor size, cm (n = 3980)	5.5 (4.5; 0.2–29.0)	8.4 (8.0; 0.3–24.5)	<0.001
Sex:	No. (%)		
Female	863 (35)	448 (29)	<0.001
Male	1614 (65)	1093 (71)	
Side of surgery:			
Right	1386 (56)	737 (48)	<0.001
Left	1091 (44)	804 (52)	
Tumor location (n = 3115):			
Upper pole	624 (34)	605 (47)	<0.001
Lower pole	656 (36)	275 (21)	
Mid-section	556 (30)	409 (32)	
Tumor size, cm (n = 3980):			
≤7	1856 (76)	657 (43)	<0.001
>7	600 (24)	867 (57)	
Tumor thrombus (n = 4013)	282 (11)	453 (29)	<0.001
2010 primary tumor classification (n = 3989):			
pT1	1702 (69)	497 (32)	<0.001
pT2	305 (12)	365 (24)	
pT3	443 (18)	605 (40)	
pT4 Gerota's fascia	11 (<1)	30 (2)	
pT4 contiguous ipsilateral adrenal extension	0	31 (2)	
2010 regional lymph node involvement:			
pNX	2174 (88)	984 (64)	<0.001
pN0	219 (9)	417 (27)	
pN1	84 (3)	140 (9)	
Tumor classification (n = 3996):			
M0 local	1918 (78)	746 (49)	<0.001
M0 locally advanced	347 (14)	492 (32)	
M1	197 (8)	296 (19)	
Nuclear grade:			
1	260 (11)	85 (6)	<0.001
2	1271 (51)	565 (37)	
3	809 (33)	703 (46)	
4	137 (6)	188 (12)	

preoperatively, but concerning intraoperative findings. Therefore, of those we could evaluate, there were no incidental adrenal metastases.

Table 2 – Multivariable associations with synchronous adrenal involvement or metastases for 3087 patients

Feature	OR (95% CI)	p value
Tumor location:		
Other	1.0 (reference)	
Upper pole	2.43 (1.43–4.15)	0.001
Tumor size (1-cm increase)	1.12 (1.05–1.21)	0.001
2010 primary tumor classification [*] :		
pT1a, pT1b, pT2a, pT2b	1.0 (reference)	
pT3a	4.27 (1.89–9.68)	<0.001
pT3b	11.67 (4.69–29.05)	<0.001
pT3c, pT4 Gerota's fascia	10.52 (3.61–30.65)	<0.001
2010 regional LNI:		
pNX, pN0	1.0 (reference)	
pN1	2.07 (1.11–3.86)	0.021
Distant metastases at surgery:		
M0	1.0 (reference)	
M1	14.49 (7.75–27.09)	<0.001

OR = odds ratio; CI = confidence interval; LNI = lymph node involvement.
^{*} Tumors classified as pT4 because of contiguous extension into the ipsilateral adrenal gland were reclassified according to the 2002 classification.

3.3. Associations with asynchronous adrenal metastases

At last follow-up, 42 patients had developed asynchronous ipsilateral adrenal metastases at a mean of 5.1 yr following surgery (median: 3.2; interquartile range [IQR]: 1.6–6.0; maximum: 26), and 87 patients developed asynchronous contralateral-only adrenal metastases at a mean of 5.0 yr following surgery (median: 3.4; IQR: 1.1–8.1; maximum: 25). Eighteen patients developed both ipsilateral and contralateral adrenal metastases following surgery.

The mean time to first asynchronous adrenal metastasis for the 111 patients who developed asynchronous ipsilateral or contralateral adrenal metastases was 4.8 yr (median: 3.2; IQR: 1.0–6.7; maximum: 26). Thirty-three (30%) of these asynchronous metastases were the only site of metastasis and therefore potentially salvageable. Estimated survival free of asynchronous adrenal metastases rates (95% confidence interval [CI]; number at risk) at 5, 10, and 15 yr following surgery were 97.5% (97.0–98.1; 2296), 96.4% (95.7–97.2; 1201), and 95.5% (94.5–96.4; 616), respectively.

Table 3 – Univariate associations with asynchronous adrenal metastases for 4018 patients

Feature	Univariate analysis		Multivariate analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Ipsilateral adrenalectomy	1.61 (1.11–2.33)	0.013	0.96 (0.64–1.42)	0.83
Contralateral adrenalectomy	11.81 (3.74–37.27)	<0.001	4.49 (1.35–14.99)	0.015
2010 primary tumor classification (n = 3989):				
pT1a	1.0 (reference)	<0.001	1.0 (reference)	<0.001
pT1b	3.78 (1.82–7.83)	<0.001	3.49 (1.67–7.28)	0.001
pT2a	5.00 (2.25–11.13)	<0.001	3.85 (1.70–8.74)	0.008
pT2b	5.24 (2.07–13.29)	<0.001	3.66 (1.40–9.56)	<0.001
pT3a	9.28 (4.62–18.65)	<0.001	4.92 (2.31–10.45)	0.001
pT3b	10.58 (4.16–26.90)	<0.001	5.31 (1.95–14.49)	0.024
pT3c, pT4	12.77 (39995–40.91)		4.20 (1.21–14.59)	
2010 regional LNI:				
pNX, pN0	1.0 (reference)		1.0 (reference)	0.81
pN1	2.58 (1.12–5.92)	0.026	0.90 (0.38–2.13)	
Nuclear grade:				
1, 2	1.0 (reference)		1.0 (reference)	
3	3.32 (2.19–5.03)	<0.001	2.17 (1.38–3.42)	<0.001
4	9.05 (4.97–16.48)	<0.001	4.66 (2.37–9.13)	<0.001
Distant metastases at surgery:				
M0	1.0 (reference)		1.0 (reference)	
M1	5.96 (3.73–9.54)	<0.001	2.50 (1.47–4.23)	<0.001
Synchronous ipsilateral adrenal involvement	3.90 (1.23–12.39)	0.021	–	–
Synchronous contralateral adrenal metastases	5.54 (0.77–39.90)	0.09	–	–
Synchronous adrenal involvement or metastases	3.44 (1.08–10.92)	0.036	–	–
Tumor location (n = 3115):				
Other	1.0 (reference)		–	–
Upper pole	0.75 (0.49–1.15)	0.18	–	–
RCC histologic subtype:				
Papillary, chromophobe	1.0 (reference)		–	–
Clear cell, collecting duct, not otherwise specified	3.53 (1.72–7.25)	<0.001	–	–
Tumor size (1-cm increase; n = 3980)	1.15 (1.11–1.20)	<0.001	–	–
Tumor size, cm (n = 3980):				
≤7	1.0 (reference)		–	–
>7	3.56 (2.42–5.23)	<0.001	–	–

HR = hazard ratio; CI = confidence interval; LNI = lymph node involvement; RCC = renal cell carcinoma.

* Multivariable models were developed using a stepwise selection procedure, with the p value for a feature to enter or leave the model set at 0.05.

Univariate and multivariate associations of clinical, surgical, and pathologic features with asynchronous adrenal metastases are summarized in Table 3. On multivariate analysis, after adjusting for known confounding pathologic

features, ipsilateral adrenalectomy was not statistically significantly associated with asynchronous adrenal metastases (hazard ratio [HR]: 0.96; p = 0.83).

3.4. Asynchronous adrenal metastases among patients without ipsilateral or contralateral adrenalectomy

Of the 4018 patients under study, 2470 (61%) did not undergo synchronous ipsilateral or contralateral adrenalectomy. Of these, 37 developed asynchronous ipsilateral adrenal metastases at a mean of 5.5 yr (median: 3.3; IQR: 1.6–6.3; maximum: 26), and 37 developed asynchronous contralateral adrenal metastases at a mean of 5.4 yr (median: 4.0; IQR: 1.3–8.3; maximum: 25). Seventeen patients developed both ipsilateral and contralateral adrenal metastases following surgery. Estimated survival free of asynchronous ipsilateral or contralateral adrenal metastases is identical (Fig. 1).

3.5. Asynchronous contralateral adrenal metastases

Estimated survival free of asynchronous contralateral adrenal metastases rates for patients with various tumor characteristics are summarized in Table 4.

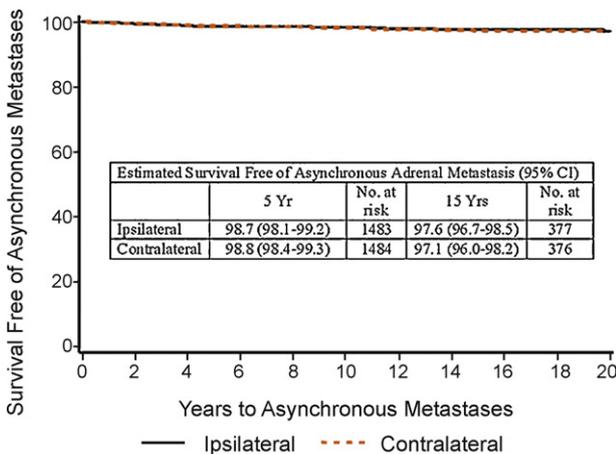


Fig. 1 – Risk of ipsilateral or contralateral asynchronous adrenal metastasis in 2470 patients undergoing surgery for renal cell carcinoma. CI = confidence interval.

Table 4 – Estimated survival free of asynchronous contralateral adrenal metastases in patients with normal contralateral adrenal gland at surgery (n = 3999)

Perioperative feature	Total	Event	Survival rate (95% CI)			
			5 yr	10 yr	15 yr	20 yr
M0 locally advanced	837	33	95.2 (93.3–97.0)	93.3 (90.9–95.8)	92.5 (89.6–95.4)	92.5 (89.6–95.4)
>7 cm	1451	55	95.5 (94.1–96.8)	93.8 (92.1–95.6)	92.7 (90.6–94.9)	92.7 (90.6–94.9)
Upper pole	1223	26	98.1 (97.1–99.0)	97.2 (96.0–98.4)	96.6 (95.2–98.1)	96.1 (94.4–97.9)
Tumor thrombus	722	23	94.8 (92.5–97.1)	93.6 (90.9–96.4)	93.6 (90.9–96.4)	93.6 (90.9–96.4)
Tumor thrombus:						
Level 0	462	14	95.7 (93.3–98.2)	94.2 (91.0–97.5)	94.2 (91.0–97.5)	94.2 (91.0–97.5)
Level 1, 2, 3, 4	251	9	92.4 (87.3–97.7)	92.4 (87.3–97.7)	92.4 (87.3–97.7)	92.4 (87.3–97.7)

CI = confidence interval.

Table 5 – Multivariable associations with death from renal cell carcinoma for 3833 patients

Feature	Univariate analysis		Multivariate analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Ipsilateral adrenalectomy	2.55 (2.27–2.87)	<0.001	1.08 (0.95–1.22)	0.24
Contralateral adrenalectomy	2.86 (1.48–5.51)	0.002	0.58 (0.30–1.12)	0.11
Age at surgery (10-yr increase)	1.04 (0.99–1.10)	0.09	1.12 (1.06–1.18)	<0.001
Constitutional symptoms at diagnosis (n = 3862)	2.96 (2.63–3.32)	<0.001	1.49 (1.32–1.68)	<0.001
Type of surgery:				
Partial	1.0 (reference)		1.0 (reference)	
Radical	9.97 (7.16–13.90)	<0.001	1.82 (1.27–2.60)	0.001
Type of surgery:				
Laparoscopic	1.0 (reference)		1.0 (reference)	
Open	2.90 (1.90–4.42)	<0.001	1.55 (1.01–2.38)	0.044
RCC histologic subtype:				
Papillary, chromophobe	1.0 (reference)		1.0 (reference)	
Clear cell, collecting duct, not otherwise specified	3.25 (2.61–4.03)	<0.001	1.89 (1.51–2.37)	<0.001
2010 primary tumor classification (n = 3841):				
pT1a	1.0 (reference)		1.0 (reference)	
pT1b	5.25 (3.76–7.32)	<0.001	3.57 (2.53–5.02)	<0.001
pT2a	10.97 (7.84–15.35)	<0.001	5.30 (3.71–7.57)	<0.001
pT2b	15.51 (10.93–22.03)	<0.001	6.72 (4.62–9.76)	<0.001
pT3a	23.46 (17.21–31.97)	<0.001	6.14 (4.37–8.62)	<0.001
pT3b	38.46 (27.44–53.92)	<0.001	7.87 (5.41–11.44)	<0.001
pT3c, pT4	51.32 (35.59–73.99)	<0.001	7.69 (5.14–11.51)	<0.001
2010 regional LNI:				
pNX, pN0	1.0 (reference)		1.0 (reference)	
pN1	7.11 (6.04–8.36)	<0.001	2.09 (1.75–2.49)	<0.001
Distant metastases at surgery:				
M0	1.0 (reference)		1.0 (reference)	
M1	10.73 (9.47–12.15)	<0.001	4.12 (3.59–4.73)	<0.001
Nuclear grade:				
1, 2	1.0 (reference)		1.0 (reference)	
3	4.81 (4.16–5.55)	<0.001	1.75 (1.48–2.08)	<0.001
4	16.19 (13.56–19.33)	<0.001	1.94 (1.47–2.55)	<0.001
Coagulative tumor necrosis (n = 3868)	4.47 (3.98–5.03)	<0.001	1.53 (1.32–1.76)	<0.001
Sarcomatoid differentiation	8.30 (6.96–9.89)	<0.001	1.82 (1.40–2.35)	<0.001
Tumor classification (n = 3848):				
M0 local	1.0 (reference)		–	–
M0 locally advanced	6.55 (5.65–7.60)	<0.001		
M1	22.34 (19.16–26.04)	<0.001		

HR = hazard ratio; CI = confidence interval; RCC = renal cell carcinoma; LNI = lymph node involvement.
* Multivariable models were developed using a stepwise selection procedure, with the p value for a feature to enter or leave the model set at 0.05.

3.6. Associations with death from renal cell carcinoma

At last follow-up, 2459 patients died at a mean of 6.6 yr following surgery. Among the 1559 patients still alive at last follow-up, the mean duration of follow-up was 10.2 yr (median: 8.2). Of the 3869 patients with known cause of

death, 1162 died from RCC at a mean of 3.6 yr following surgery (median: 1.9; IQR: 0.8–4.9; maximum: 28).

Univariate and multivariate associations of clinical, surgical, and pathologic features with death from RCC are summarized in Table 5. On multivariate analysis, after adjusting for known confounding clinical and pathologic

features, ipsilateral adrenalectomy (HR: 1.08; $p = 0.24$) and contralateral adrenalectomy (HR: 0.58; $p = 0.11$) were no longer statistically significantly associated with death from RCC.

In the 95 patients with synchronous adrenal involvement, the estimated CSS rates (95% CI, number at risk) at 1, 3, and 5 yr following surgery were 44.2% (35.1–55.7; 40), 23.0% (15.7–33.6; 20), and 14.6% (8.8–24.3; 11). However, there were 11 patients with >5 yr of survival beyond surgery, including 3 who are still alive with no evidence of disease at last follow-up (maximum: 18.5 yr).

4. Discussion

The historical rationalization of concomitant removal of the adrenal gland in patients with RCC has been the removal of cancerous cells (either micro- or macroscopic) within the adrenal gland that may eventually lead to difficulty for the patient. If the incidence of adrenal involvement at the time of renal surgery is high, as formerly reported [3], adrenalectomy may be justified, but we have observed that in the current series, the adrenal gland is rarely involved—particularly in tumors ≤ 7 cm in size (0.5%). We note that 80% of all new renal cancers in the United States are ≤ 7 cm in size [20]. Consequently, the practice of routine adrenalectomy in the average patient today would unnecessarily remove nearly 199 normal adrenal glands for every one involved with RCC. With the recently updated European Association of Urology guidelines on RCC no longer recommending routine adrenalectomy [21], most experts now only call for routine ipsilateral adrenalectomy in “high-risk: patients [9,18]. However, we find that even in patients with high-risk features for synchronous adrenal involvement (Table 2), such as tumors >7 cm, pT category 3 or 4, tumor thrombus, or upper-pole tumors, the frequency of ipsilateral adrenal involvement is still quite low ($\leq 10\%$).

The issue, arguably more important than incidence of ipsilateral adrenal involvement, is subsequent cancer control. If routine ipsilateral adrenalectomy in high-risk patients removes micrometastatic disease and prevents death from subsequent RCC progression, this alone would be reason to recommend it. However, we did not find that synchronous ipsilateral adrenalectomy lowers the risk of subsequent adrenal metastasis, nor did it improve CSS on multivariate analysis (Tables 3 and 5). Furthermore, we note that the risk of asynchronous adrenal metastasis is just as likely to occur in the contralateral adrenal gland as in the ipsilateral adrenal gland. Therefore, if the rationale for removing the ipsilateral adrenal gland is to remove micrometastasis, then by the same token, our data suggest that the surgeon would be obligated to remove the contralateral adrenal gland, as well. A more prudent policy appears to be sparing the ipsilateral adrenal gland unless involved by radiographic or intraoperative criteria. When an asynchronous adrenal metastasis occurs, 30% of the time, it is the only site of disease and therefore often salvageable by a second surgery [22].

The length of follow-up and the large number of participants in our study allows us to determine a fairly accurate risk of asynchronous adrenal metastasis in this

cohort. This rate is actually higher than previous reports and can occur up to 26 yr after initial surgery. Prior to this manuscript, only 60 cases were reported in the literature up to 2003 [22], which erroneously conveyed the idea that the contralateral adrenal gland was rarely involved [7,9]. In this cohort alone, we report on 147 cases of asynchronous metastases (3.7%), of which 105 cases were contralateral asynchronous metastases (2.6%). Interestingly, an autopsy study found a nearly identical percentage of patients having a contralateral metastasis after nephrectomy [23]. Ironically, these “high-risk” patients, in whom routine adrenalectomy has been proposed, may be the very patients in whom we should strive hardest to preserve the adrenal gland; these patients are at highest risk for a subsequent asynchronous metastasis (Table 4). For example, a policy of routine adrenalectomy in all patients with renal cell tumors >7 cm would find an approximately 5% rate of synchronous adrenal involvement. At 10 yr in this same cohort, approximately 6% will develop a contralateral asynchronous adrenal metastasis in a solitary adrenal gland and face untreated cancer versus total adrenal insufficiency (6.2%; 95% CI, 4.4–7.9).

Theoretically, adrenalectomy will be beneficial in only the right circumstances. If the disease is very low risk, the risk of adrenal involvement will be so low that the number needed to treat would be too high to merit routine use. In very high-risk patients, the disease will be driven by biology, and the resection of the adrenal gland is unlikely to affect survival. Some have gone so far as to suggest that surgery in patients with synchronous adrenal involvement may be futile [24]. Though we agree that most will not be cured by surgical resection, we found that 12% will survive at least 5 yr and 4.2% appear to be cured by surgery. We also believe that it is important to achieve maximum local tumor control not only for staging purposes but to serve to prepare the patient for ongoing clinical trials of adjuvant systemic treatment.

This study is limited by the single-institution, retrospective nature of the study design. The patients were not randomized to adrenalectomy, and therefore, the analysis is subject to confounding. However, because it is unlikely that a randomized trial of adrenalectomy versus no adrenalectomy will be performed (nor do we advise that it should be), we believe that quality cohort studies will provide the best information available on the effect of adrenal involvement with RCC.

5. Conclusions

Ipsilateral adrenal involvement from RCC was uncommon even in large, locally advanced, and/or upper-pole tumors. Routine ipsilateral adrenalectomy in patients with high-risk features does not appear to offer any oncologic benefit, while placing a significant portion of patients at risk for a metastasis in a solitary adrenal gland. Adrenalectomy should only be performed with radiographic or intraoperative evidence of adrenal involvement.

Author contributions: Bradley C. Leibovich had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Weight, Leibovich, Kim.

Acquisition of data: Lohse, Cheville, Leibovich, Thompson.

Analysis and interpretation of data: Lohse, Weight, Leibovich.

Drafting of the manuscript: Weight, Lohse, Leibovich.

Critical revision of the manuscript for important intellectual content:

Thompson, Kim, Boorjian, Cheville.

Statistical analysis: Lohse, Weight.

Obtaining funding: None.

Administrative, technical, or material support: Lohse.

Supervision: Leibovich.

Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

References

- [1] Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *J Urol* 1969;101:297–301.
- [2] Skinner DG, Colvin RB, Vermillion CD, Pfister RC, Leadbetter WF. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. *Cancer* 1971;28:1165–77.
- [3] Angervall L, Wahlqvist L. Follow-up and prognosis of renal carcinoma in a series operated by perifascial nephrectomy combined with adrenalectomy and retroperitoneal lymphadenectomy. *Eur Urol* 1978;4:13–7.
- [4] Mickisch G, Carballido J, Hellsten S, Schulze H, Mensink H. Guidelines on renal cell cancer. *Eur Urol* 2001;40:252–5.
- [5] Nguyen MM, Gill IS, Ellison LM. The evolving presentation of renal carcinoma in the United States: trends from the Surveillance, Epidemiology, and End Results Program. *J Urol* 2006;176:2397–400.
- [6] Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst* 2006;98:1331–4.
- [7] Lane BR, Tiong HY, Campbell SC, et al. Management of the adrenal gland during partial nephrectomy. *J Urol* 2009;181:2430–7.
- [8] Leibovitch I, Raviv G, Mor Y, Nativ O, Goldwasser B. Reconsidering the necessity of ipsilateral adrenalectomy during radical nephrectomy for renal cell carcinoma. *Urology* 1995;46:316–20.
- [9] 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;181:2009–17.
- [10] 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;97:505–8.
- [11] De Sio M, Autorino R, Di Lorenzo G, et al. Adrenalectomy: defining its role in the surgical treatment of renal cell carcinoma. *Urol Int* 2003;71:361–7.
- [12] Gill IS, McClennan BL, Kerbl K, et al. Adrenal involvement from renal cell carcinoma: predictive value of computerized tomography. *J Urol* 1994;152:1082–5.
- [13] Kletscher BA, Qian J, Bostwick DG, Blute ML, Zincke H. Prospective analysis of the incidence of ipsilateral adrenal metastasis in localized renal cell carcinoma. *J Urol* 1996;155:1844–6.
- [14] Moudouni SM, En-Nia I, Patard JJ, Manunta A, Guille F, Lobel B. Real indications for adrenalectomy in renal cell carcinoma. *Scand J Urol Nephrol* 2002;36:273–7.
- [15] Tsui KEH, Shvarts O, Barbaric Z, Figlin R, Dekernion JB, Beldegrun A. Is adrenalectomy a necessary component of radical nephrectomy? UCLA experience with 511 radical nephrectomies. *J Urol* 2000;163:437–41.
- [16] Wunderlich H, Schlichter A, Reichelt O, et al. Real indications for adrenalectomy in renal cell carcinoma. *Eur Urol* 1999;35:272–6.
- [17] Campbell SC, Novick AC, Bukowski RM. Renal tumors. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. *Campbell-Walsh Urology*. ed. 9 Philadelphia, PA: Saunders Elsevier; 2007. p. 1567–637.
- [18] Novick AC. Open surgery of the kidney. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. *Campbell-Walsh Urology*. ed. 9 Philadelphia, PA: Saunders Elsevier; 2007. p. 1686–758.
- [19] Siemer S, Lehmann J, Kamradt J, et al. Adrenal metastases in 1,635 patients with renal cell carcinoma: outcome and indication for adrenalectomy. *J Urol* 2004;171:2155–9.
- [20] Miller DC, Ruterbusch J, Colt JS, et al. Contemporary clinical epidemiology of renal cell carcinoma: insight from a population based case-control study. *J Urol* 2010;184:2254–8.
- [21] Ljungberg B, Cowan NC, Hanbury DC, et al. EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol* 2010;58:398–406.
- [22] Lau WK, Zincke H, Lohse CM, Cheville JC, Weaver AL, Blute ML. Contralateral adrenal metastasis of renal cell carcinoma: treatment, outcome and a review. *BJU Int* 2003;91:775–9.
- [23] Saitoh H, Hida M, Nakamura K. Metastatic processes and a potential indication of treatment for metastatic lesions of renal adenocarcinoma. *J Urol* 1982;128:916–8.
- [24] von Knobloch R, Schrader AJ, Walthers EM, Hofmann R. Simultaneous adrenalectomy during radical nephrectomy for renal cell carcinoma will not cure patients with adrenal metastasis. *Urology* 2009;73:333–6.