



## Risk Factors for Adrenal Invasion in Renal Cell Carcinoma

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<sup>1</sup>Dokuz Eylül University Faculty of Medicine, Department of Urology, İzmir, Turkey

<sup>2</sup>Dokuz Eylül University Faculty of Medicine, Department of Patology, İzmir, Turkey

### Abstract

**Objective:** In this study, we aimed to describe the risk factors associated with adrenal invasion in patients who were diagnosed with renal cell carcinoma (RCC) after radical nephrectomy and identify which risk factors are indications for ipsilateral adrenalectomy (IA).

**Materials and Methods:** Preoperative (age, gender, tumor side and location, presence of lung metastasis), intraoperative (thrombectomy rate, IA and additional surgery rate), and histopathological data of 298 patients with RCC were reviewed. The patients were divided into 2 groups, those with adrenal invasion and those without, and patient data were compared between these groups. Subsequently, rates of renal sinus invasion, perinephric invasion, and renal vein invasion were evaluated in the T3-4 and T3a patient group and the relationship between these rates and adrenal invasion was investigated.

**Results:** Adrenal invasion was detected in 8 (2.7%) of the patients. There were no significant relationships between adrenal invasion and age, gender, tumor side, tumor location, surgery duration, thrombectomy rate, disease stage, sarcomatoid features, microvascular invasion, collecting system invasion, tumor necrosis, or renal vein invasion. The presence of adrenal invasion was associated with a higher rate of additional intraoperative interventions. Adrenal invasion was also significantly associated with greater tumor size, higher pathologic T (pT) stage, and rates of lung metastasis, perinephric invasion, and renal sinus invasion. When stage pT3-4 and pT3a patients were evaluated separately, no significant relation was found between adrenal invasion and renal sinus invasion, perinephric invasion, or renal venous invasion.

**Conclusion:** pT stage, presence of pulmonary metastasis, and renal sinus invasion were important risk factors for adrenal invasion.

**Keywords:** Renal cell carcinoma, adrenal invasion, adrenalectomy, radical nephrectomy

### Introduction

Renal cell carcinoma (RCC), which accounts for 2-3% of all cancer cases, is the most common malignant tumor of the kidney (1). Ipsilateral adrenalectomy (IA) with radical nephrectomy was first described by Robson et al. (2) in 1969 to correctly determine the size and spread of the tumor and to improve oncological outcomes in RCC. Later, IA continued to be practiced with radical nephrectomy in order to achieve a wide, intact surgical margin (3). In response to this practice, Lane et al. (4) demonstrated in their study that IA did not significantly impact 5- and 10-year disease-specific or overall survival. In subsequent studies it was reported that the rate of adrenal invasion in patients who

undergo nephrectomy with IA is 1-4% (5,6,7). Therefore, routine IA during nephrectomy is not recommended in these studies, but IA is recommended for patients whose radiological images suggest a large tumor, an upper pole tumor, or adrenal invasion (5,6,7,8). These recommendations indicate that the practice of IA has changed over the years based on the risk-benefit ratio for the patient. However, even if the rate of adrenal invasion is 1-4%, we believe that predicting adrenal invasion provides information that is important for correctly staging patients, gaining insight into prognosis, and creating adjunct therapy and follow-up protocols. Because reducing tumor burden is a facet of RCC treatment, resecting an adrenal gland that has invasion/

metastasis becomes even more important. Therefore, in this study we aimed to identify patient risk factors associated with adrenal invasion and to determine which risk factors constitute indications for IA.

## Materials and Methods

Patients who underwent radical nephrectomy between 1995 and 2013 were retrospectively evaluated. Those with a histopathological diagnosis of RCC were included in the study. A total of 298 patients with RCC were evaluated based on preoperative data (age, sex, tumor side, tumor location, presence of lung metastasis), intraoperative data (thrombectomy, IA, and other procedures), and histopathological data [pathological T (pT) stage, Fuhrman grade, sarcomatoid features, adrenal invasion, microvascular invasion, renal sinus invasion, perinephric invasion, collecting system invasion, tumor necrosis, renal vein and/or vena cava invasion]. The patients were divided into groups based on presence or absence of adrenal invasion and patient data were compared between the groups. The same comparisons were done within the group of patients who underwent IA. We then evaluated rates of renal sinus invasion, perinephric invasion, and renal vein invasion in the T3-4 and T3a patient groups and examined the relationship between these rates and adrenal invasion.

### Statistical Analysis

First, patient data were evaluated by comparing those with and without adrenal invasion using the Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. Kaplan-Meier survival analysis and chi-square test were used to evaluate mortality and survival between groups. Chi-square test was used to compare presence of adrenal invasion and rates of renal sinus invasion, perinephric invasion, and renal vein invasion rates in the T3-4 and T3a patient groups. The Statistical Package for the Social Sciences (SPSS version 20.0; SPSS, Chicago, Illinois, USA) was used for statistical analysis. The data were expressed as mean and standard deviation, and statistical analysis was based on median values. Results with p values  $\leq 0.05$  were considered significant.

## Results

The 298 patients who underwent radical nephrectomy had a mean age of  $59.2 \pm 11.6$  (26.5-86.4) years. Of these, 85 patients underwent IA, and 8 (2.7%) of those patients had adrenal invasion. There were no cases of adrenal metastasis. The mean follow-up period was  $52.3 \pm 35.9$  (1-185.1) months and mean overall survival was  $114.4 \pm 5.6$  months. No significant relationship was found between adrenal invasion and sex, tumor side, tumor location, operative time, thrombectomy rate, Fuhrman grade, sarcomatoid features, microvascular invasion, collecting system invasion, tumor necrosis, renal vein invasion, and vena cava invasion (Tables 1 and 2). Additional intraoperative interventions were more common in the presence of adrenal invasion. Presence of adrenal invasion was also associated with significantly greater tumor size (whole group only), pT stage, presence of lung metastasis, and rates of perinephric invasion and renal sinus invasion (Tables 1 and 2).

When pT3-4 and pT3a patients were evaluated separately, no significant relationship was observed between adrenal invasion and renal sinus invasion, perinephric invasion, or renal vein invasion (Table 3).

## Discussion

Performing IA at the time of radical nephrectomy has been a topic of debate for over 25 years (9). The rate of ipsilateral adrenal invasion in patients who undergo radical nephrectomy for RCC is reported to be  $<4\%$  (5,6,7). The rate of adrenal invasion in our study was 2.7%. Current guidelines state that IA during radical nephrectomy does not confer a survival advantage in patients without radiological or intraoperative signs of adrenal invasion and is therefore not recommended for these patients (10).

In a randomized study of 40 patients investigating the perioperative complications of IA in radical nephrectomy, no significant difference was seen in operative time or postoperative complications (11). In our study, the presence of adrenal invasion did not significantly affect operative time.

Many risk factors for predicting adrenal invasion have been identified. It was reported that upper-pole renal tumors  $>7$  cm in size may be associated with adrenal invasion (5). On the other hand, Kutikov et al. (12) pathologically examined IA specimens from 91 patients with  $>7$  cm upper-pole renal tumors and found adrenal invasion in only 4 patients (4.4%). They concluded based on their findings that upper-pole localization is not a predictive factor in RCC (12). There was no significant relationship between adrenal invasion and tumor side or location in our study. However, we observed that adrenal invasion was present in a significant proportion of patients with distant metastasis (lung). This suggests that lung metastasis rates are higher in patients with adrenal invasion due to the advanced tumor stage.

Previous studies examining whether adrenal invasion by RCC occurs via direct extension or through the renal/adrenal veins have emphasized that hematogenous spread may be more common than direct invasion. In a review evaluating this observation, it was reported that left-sided primary renal tumors were predominant (62-100%) among patients with adrenal invasion (5). It was suggested the risk of retrograde tumor embolization was higher on the left side because the adrenal vein drains into the renal vein on that side. However, the multivariate analysis results of other studies within the same review did not support the association between left-sided RCC and adrenal invasion. Due to these contradictory results, it was concluded that RCC laterality cannot be considered an independent risk factor (5). There was also no significant relationship between adrenal invasion and tumor side in our study.

pT stage has also been investigated as a risk factor for adrenal invasion. In a study by Moudouni et al. (13) involving 210 patients, adrenal invasion was detected in 15 patients, 13 of whom were stage T3-4. Similarly, 70% of the patients with adrenal invasion in our study had at least stage pT3a tumors. When pT3-4 and pT3a patients with renal sinus invasion, renal vein invasion, and perinephric invasion were evaluated

Table 1. Analysis of possible risk factors in patients with and without adrenal invasion				
		Adrenal invasion (-) (n=290)	Adrenal invasion (+) (n=8)	p
Age (years)		59.2±11.6	59.6±10.1	0.924
Gender	Female	95	3	0.721
	Male	195	5	
Operative time (minutes)		165.2±61.4	183.8±43.7	0.219
Tumor size (mm)		67.2±32	98.1±39.4	0.014
Tumor side	Right	143	3	0.510
	Left	147	5	
Tumor location	Upper pole	102	3	0.412
	Mid-pole	95	1	
	Lower pole	93	4	
Lung metastasis	(-)	274	5	0.000
	(+)	16	3	
Thrombectomy	(+)	12	1	0.253
	(-)	278	7	
Additional intraoperative procedure	(+)	18	3	0.01
	(-)	272	5	
Pathological stage	T1a	70	0	0.012
	T1b	75	0	
	T2a	52	1	
	T2b	21	1	
	T3a	47	2	
	T3b	15	1	
	T3c	1	0	
	T4	9	3	
Fuhrman grade	1	45	0	0.077
	2	131	2	
	3	60	4	
	4	28	1	
Sarcomatoid features	(+)	19	1	0.507
	(-)	271	7	
Microvascular invasion	(+)	43	2	0.428
	(-)	247	6	
Renal sinus invasion	(+)	23	4	0.003
	(-)	267	4	
Collecting system invasion	(+)	8	1	0.112
	(-)	282	7	
Tumor necrosis	(+)	14	1	0.342
	(-)	276	7	
Pathologic renal vein invasion	(+)	25	1	0.701
	(-)	265	7	
Pathologic vena cava invasion	(+)	4	0	0.738
	(-)	286	8	
Perinephric invasion	(+)	48	5	0.001
	(-)	242	3	
Overall mortality		70 (24.1%)	5 (62.5%)	0.014
Overall survival (months)		116.1±5.7	30.1±9.2	<0.001

<b>Table 2. Possible risk factors for adrenal invasion in patients who underwent adrenalectomy</b>				
		<b>Adrenal invasion (-) (n=77)</b>	<b>Adrenal invasion (+) (n=8)</b>	<b>p</b>
Age (years)		58.4±12	59.6±10.1	0.741
Gender	Female	27	3	0.891
	Male	50	5	
Operative time (minutes)		178±61.4	183.8±43.7	0.556
Tumor size (mm)		82±35.6	98.1±39.4	0.197
Tumor side	Right kidney	34	3	0.718
	Left kidney	43	5	
Tumor location	Upper pole	34	3	0.519
	Mid-pole	19	1	
	Lower pole	24	4	
Lung metastasis	(-)	74	5	<0.001
	(+)	3	3	
Thrombectomy	(+)	8	1	0.854
	(-)	69	7	
Additional intraoperative procedures	(+)	8	3	0.030
	(-)	69	5	
Pathological stage	T1a	5	0	0.012
	T1b	15	0	
	T2a	21	1	
	T2b	10	1	
	T3a	17	2	
	T3b	6	1	
	T3c	1	0	
	T4	2	3	
Fuhrman grade	1	11	0	0.268
	2	34	2	
	3	18	4	
	4	9	1	
Sarcomatoid features	(+)	8	1	0.854
	(-)	69	7	
Microvascular invasion	(+)	19	2	0.984
	(-)	58	6	
Renal sinus invasion	(+)	11	4	0.012
	(-)	66	4	
Collecting system invasion	(+)	3	1	0.274
	(-)	74	7	
Tumor necrosis	(+)	5	1	0.528
	(-)	72	7	
Pathologic renal vein invasion	(+)	12	1	0.818
	(-)	65	7	
Pathologic vena cava invasion	(+)	4	0	0.509
	(-)	73	8	
Perinephric invasion	(+)	17	5	0.013
	(-)	60	3	
Overall mortality		16 (20.8%)	5 (62.5%)	0.009
Overall survival (months)		131±11.8	30.1±9.2	<0.001

**Table 3. Analysis of pathologic T3-4 patients in terms of perinephric, renal sinus, and renal vein invasion**

T3a patients (n=49)		Adrenal invasion (-) (n=47)	Adrenal invasion (+) (n=2)	p
Perinephric invasion	(+)	34	1	0.493
	(-)	13	1	
Renal sinus invasion	(+)	18	2	0.082
	(-)	29	0	
Renal vein invasion	(+)	10	0	0.465
	(-)	37	2	
T3-4 patients (n=78)		Adrenal invasion (-) (n=72)	Adrenal invasion (+) (n=6)	p
Perinephric invasion	(+)	48	5	0.401
	(-)	24	1	
Renal sinus invasion	(+)	23	3	0.367
	(-)	49	3	
Renal vein invasion	(+)	24	0	0.089
	(-)	48	6	

in separate subgroups, all groups had similar rates of adrenal invasion. These results suggest that pT3-4 is a risk factor for adrenal invasion, whereas renal sinus, renal vein, and perinephric invasion do not effectively discriminate adrenal invasion on their own. However, the nonsignificance of our findings may be due to the small numbers of patients with adrenal invasion and in the subgroups, which is one of the limitations of this study. When we examined pathological data other than T stage, we observed no significant association between adrenal invasion and Fuhrman grade, sarcomatoid features, microvascular invasion, collecting system invasion, tumor necrosis, renal vein invasion, or vena cava invasion. Our findings indicate that adrenal invasion is more common only in the presence of perinephric and renal sinus invasion. The possible pathophysiology of this may be related to the higher risk of metastasis in RCC due to the presence of ample venous and lymphatic drainage in the renal sinus (14). However, our review of the literature yielded no study that shows a direct association between adrenal invasion and pathological data other than T stage, especially renal sinus invasion. Perinephric invasion and renal sinus invasion may be signs of advanced disease, which could explain their significant relationship with adrenal invasion. Other than this, overall survival times were lower and mortality rates were higher in patients with adrenal invasion compared to the other patients. This finding is also related to advanced T stage.

#### Study Limitations

Cancer-specific survival and metastasis-free survival were not assessed in this study. Due to the adrenal preserving approach developed over the years, the long-term, retrospective nature of the study and the small patient population (especially in the group with adrenal invasion) constitute limitations of this research.

## Conclusion

In summary, the findings of this study indicate that pT stage and the presence of lung metastasis and renal sinus invasion constitute important risk factors for adrenal invasion. However, the necessity of IA in patients with risk factors for adrenal involvement is debatable. It is clear that more extensive prospective studies are needed to bring clarity to this issue.

## Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: O.B., Ö.D., G.A., İ.Ç., Concept: K.Ç., S.Ç., Design: K.Ç., S.Ç., K.Y., Data Collection or Processing: K.Ç., S.Ç., Analysis or Interpretation: K.Ç., S.Ç., K.Y., Literature Search: K.Ç., S.Ç., Writing: K.Ç.

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