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Factors Affecting Adrenal Gland Involvement in Patients Who Underwent Radical Nephrectomy for Renal Cell Carcinoma

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Aim: We investigated pathological characteristics of adrenal involvement in patients who underwent radical nephrectomy (RN) for renal cell carcinoma (RCC).

Materials and Methods: 49 patients (34 male, 15 female) who underwent RN and simultaneous ipsilateral adrenalectomy due to RCC were included. Patient and tumor characteristics, histopathologic features, disease stage, and radiologic computerized tomography (CT) features were studied in order to see if any of them are associated with pathological evidence of adrenal involvement.

Results: Presence of adrenal irregularity ($P = 0.002$), venous thrombosis ($P = 0.010$), tumor necrosis ($P = 0.031$), and lymph node (LN) involvement ($P = 0.013$) on CT, increased Fuhrman grade ($P = 0.037$), and presence of capsular invasion ($P = 0.027$) and perirenal fatty tissue invasion by RCC ($P = 0.011$) were found to be significantly associated with ipsilateral adrenal involvement. There was no statistically significant association with location of the tumor in the upper pole of the kidney ($P = 0.077$), increased tumor size ($P = 0.098$), pathologic stage ($P = 0.085$), presence of vascular invasion ($P = 0.067$), and metastasis despite higher incidence of them in the group with adrenal involvement.

Conclusions: Risk factors for ipsilateral adrenal involvement by RCC appear to be the presence of adrenal gland irregularity, venous thrombosis and necrosis on CT, increased Fuhrman grade, presence of capsular and peripheral fatty tissue invasion, LN involvement, and metastasis. Therefore, we recommend ipsilateral adrenalectomy particularly in this patient group.

Key Words: Renal cancer, adrenal involvement, risk factors

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Renal Hücreli Karsinom Nedeni ile Radikal Nefrektomi Yapılan Hastalarda Adrenal Bezi Tutulumunu Etkileyen Faktörler

Amaç: Bu çalışmada renal hücreli karsinom (RHK) nedeniyle radikal nefrektomi (RN) yaptığımız olgularda adrenal tutulumun patolojik özellikleri incelenmiştir.

Yöntem ve Gereç: RHK nedeniyle RN ve ipsilateral adrenalectomi yaptığımız 49 olgu (34 erkek, 15 bayan) çalışmaya alınmıştır. Hasta ve tümör özellikleri, histopatolojik bulgular, hastalık evresi ve bilgisayarlı tomografi (BT) bulguları değerlendirilerek patolojik olarak adrenal tutulum ile ilişkileri araştırılmıştır.

Bulgular: BT'de adrenal düzensizlik ($P = 0.002$), venöz trombus ($P = 0.010$), tümör nekrozu ($P = 0.031$), lenf nodu (LN) tutulumu ($P = 0.013$) olması; artmış Fuhrman derecesi ($P = 0.037$), kapsüler invazyon ($P = 0.027$) ve perirenal yağ dokusu invazyonu ($P = 0.011$) olması, ipsilateral adrenal tutulumu ile anlamlı olarak ilişkili bulunmuştur. Tümörün böbrek üst polde yerleşmesi ($P = 0.077$), artmış tümör boyutu ($P = 0.098$), patolojik evre ($P = 0.085$), vasküler invazyon varlığı ($P = 0.067$) ve metastaz varlığı, her ne kadar adrenal tutulumu olan grupta artmış olarak saptansa da istatistiksel olarak anlamlı bulunmamıştır.

Sonuç: BT'de adrenal düzensizlik, venöz trombus, nekroz varlığı, artmış Fuhrman derecesi, kapsüler invazyon, perirenal yağ dokusu invazyonu, LN tutulumu ve metastaz varlığı ipsilateral adrenal tutulumu için risk faktörleridir. Bu hastalarda RN ile birlikte ipsilateral adrenalectomi yapılmasını öneriyoruz.

Anahtar Sözcükler: Renal kanser, adrenal tutulum, risk faktörleri

Introduction

Renal cell carcinoma (RCC) accounts for 3% of all adult solid tumors (1) and radical nephrectomy (RN) with ipsilateral adrenalectomy has been the standard for its surgical treatment, which was first described by Robson in 1963 (2). Currently, most of the RCCs are being detected incidentally by their smaller size due to improved radiologic

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imaging modalities and their frequent use leading to increased RCC incidence worldwide (3) at an earlier stage and with less associated lymph node and adrenal involvement (4). Therefore, there is a tendency to perform nephron sparing surgery (NSS) rather than RN in suitable kidney tumors (5).

Malignant involvement of the ipsilateral adrenal gland by RCC has been reported to be between 1% and 10% of RN specimens and up to 23% in autopsy series (6). Therefore, unnecessary removal of the adrenal gland seems to be overtreatment in almost 90% of cases. Preassessment of the adrenal gland and definition of risk factors associated with adrenal involvement is important for the urologist, which could prevent unnecessary adrenalectomies. In this regard, we retrospectively investigated factors affecting adrenal gland involvement in patients who underwent RN for RCC, its incidence, and preoperative computerized tomography (CT) findings, which might allow the surgeon to select patients for adrenal sparing surgery.

Materials and Methods

Between 2004 and 2007, 49 patients (34 male, 15 female) who underwent RN and simultaneous ipsilateral adrenalectomy due to renal cancer were included in our study. Diagnosis of RCC was confirmed histopathologically in all patients. Mean patient age was 57 years (range, 19-88), and 34 (69%) patients were males and 15 (31%) were females. All patients have undergone preoperative abdominal ultrasound (USG), CT, and chest X-ray for staging. We performed NSS in patients with a kidney mass of <4 cm in size therefore, we did not include these patients in our study. RN was performed with adrenalectomy and retroperitoneal lymph node (LN) dissection at the level of renal hilus in all patients. If pathologic enlarged LNs are detected on preoperative CT or intraoperatively then lymphadenectomy was extended to include paracaval and interaortacaval lymph nodes for right sided tumors and para-aortic lymph nodes for left sided tumors.

We retrospectively reviewed the patient charts regarding the following parameters: patient demographics (gender and age), tumor characteristics (tumor localization, laterality, and size), histopathologic features (histologic type, Fuhrman grade, presence of capsular invasion, peripheral fatty tissue invasion, and

vascular invasion), disease stage (pathologic stage, presence of LN involvement, and metastasis), and radiologic findings on CT (presence of adrenal gland abnormalities, tumor necrosis, and venous thrombosis) and how they correlate with adrenal involvement was investigated.

On CT scans, tumor laterality (right/left), tumor size (≤ 7 cm, > 7 cm), tumor localization (upper/mid/lower poles), presence of lymphadenopathy, necrosis or venous thrombosis, and adrenal gland abnormalities (irregularity, enlarged diameter, mass lesion, heterogeneous density, contiguous infiltration) were noted. Preoperative CT findings were compared with histopathologic results in order to evaluate the accuracy of CT in detecting adrenal involvement by RCC.

Pathologic staging was performed according to the histopathologic examination of the tumor with the evaluation of renal capsule, perirenal fatty tissue, renal vein, regional lymph nodes and Gerota's fascia in terms of the presence of tumor invasion by using TNM 2002 guidelines (7). Tumor size was measured as the maximum diameter on CT scans. Capsular invasion, peripheral renal tissue (perirenal fat) invasion, and vascular invasion were also evaluated and verified microscopically.

Statistical analysis was performed using SPSS 11.5. Data regarding patient age was presented as mean \pm standard deviation and Fuhrman grade was presented as median (minimum, maximum). Significance between the groups was analyzed by Mann Whitney U test. Comparison of the categories was performed using Chi square and Fisher's exact tests. $P < 0.05$ was considered statistically significant.

Results

Renal tumors were located in the upper, mid, and lower poles of the kidneys in 51%, 31%, and 18% of cases, respectively. Of the 49 patients, 6 (12.3%) had ipsilateral adrenal involvement by RCC. No contralateral or bilateral adrenal involvement was detected by preoperative radiologic evaluation including US and CT.

There were 4 (11.8%) adrenal metastases in the males and 2 (13.3%) in the females (Table 1). No significant relationship concerning patient demographics (age and gender) was detected between the group of patients with

and without adrenal involvement ($P > 0.05$) (Table 1). Correlation between tumor characteristics (tumor localization, size, and laterality), radiologic features (adrenal gland abnormalities, presence of tumor necrosis, and venous thrombosis on CT) and adrenal involvement are summarized in Table 1. Tumor size, location, and laterality did not seem to affect adrenal involvement in our study ($P > 0.05$). However, the presence of adrenal irregularity, necrosis and venous thrombosis were found to be significant risk factors for adrenal involvement (Table 1). Presence of necrosis on CT was also confirmed histopathologically after RN in all patients. Although the presence of adrenal irregularity on CT was significantly associated with adrenal involvement (Table 1), of the 6 patients with adrenal involvement, CT did not demonstrate any abnormality despite metastasis was confirmed histopathologically in 2 patients. Therefore, CT demonstrates 66.7% sensitivity, 93.0% specificity, 57.1%

positive predictive value, and 93.0% negative predictive value for detection of adrenal involvement when correlated with pathologic examination of the adrenal glands.

Table 2 shows the correlation between histopathologic features (histologic type, Fuhrman grade, presence of capsular invasion, perirenal fat invasion, and vascular invasion) and adrenal gland involvement. Presence of capsular invasion, perirenal fat invasion, and increased Fuhrman grade were found to be significantly associated with adrenal gland involvement by RCC; however, vascular invasion and histologic tumor type were not found to be associated with adrenal involvement. Relationship between disease stage (including pathologic stage, presence of lymph node involvement, and metastasis) and adrenal gland involvement is demonstrated on Table 2. Among these variables, only the presence of LN involvement was a significant risk factor.

Table 1. Comparison of patient demographics, tumor characteristics, and radiologic findings with adrenal gland involvement. CT: Computerized tomography.

		Presence of adrenal gland involvement		P
		(-) n = 43	(+) n = 6	
Patient Demographics				
Gender	Male	30 (69.8%)	4 (66.7%)	1.000
	Female	13 (30.2%)	2 (33.3%)	
Age		58.2 ± 12.35	51.5 ± 17.9	0.247
Tumor Characteristics				
Tumor Localization	Upper pole	20 (46.5%)	5 (83.3%)	0.077
	Mid pole	15 (34.9%)	-	
	Lower pole	8 (18.6%)	1 (16.7%)	
Tumor Laterality	Right	23 (53.5%)	5 (83.3%)	0.219
	Left	20 (46.5%)	1 (16.7%)	
Tumor Size	4-7 cm	24 (55.8%)	1 (16.7%)	0.098
	>7cm	19 (44.2%)	5 (83.3%)	
Radiologic CT Findings				
Adrenal gland Irregularity	(-)	40 (93.0%)	2 (33.3%)	0.002
	(+)	3 (7.0%)	4 (66.7%)	
Presence of venous thrombosis	(-)	41 (95.3%)	3 (50%)	0.010
	(+)	2 (4.7%)	3 (50%)	
Presence of necrosis	(-)	22 (51.2%)	-	0.031
	(+)	21 (48.8%)	6 (100%)	

Table 2. Comparison of histopathologic findings and disease stage with adrenal gland involvement status. LN: Lymph node.

		Presence of adrenal gland involvement		P
		(-) n = 43	(+) n = 6	
Histopathologic Findings				
Histologic Type	Clear cell	36 (83.3%)	6 (100%)	0.371
	Papillary	16 (14%)	-	
	Chromophobe cell	1 (2.3%)	-	
Fuhrman Grade		2 (1-4)	3 (2-4)	0.037
Capsular invasion	(-)	22 (51.2%)	-	0.027
	(+)	21 (48.8%)	6 (100%)	
Perirenal fatty tissue invasion	(-)	32 (74.4%)	1 (16.7%)	0.011
	(+)	11 (25.6%)	5 (83.3%)	
Vascular invasion	(-)	37 (86%)	3 (50%)	0.067
	(+)	6 (14%)	3 (50%)	
Disease Stage				
Pathologic stage	T1a	7 (16.3%)	1 (16.7%)	0.085
	T1b	17 (39.5%)	-	
	T2	4 (9.3%)	1 (16.7%)	
	T3a	11 (25.6%)	1 (16.7%)	
	T3b	4 (9.3%)	3 (50%)	
Presence of LN involvement	(-)	43 (100%)	2 (33.3%)	0.013
	(+)	-	4 (66.7%)	
Presence of metastasis	(-)	43 (100%)	5 (83.3%)	0.122
	(+)	-	1 (16.7%)	

Discussion

RCC might involve adrenal gland and ipsilateral adrenalectomy with RN was suggested previously (2). However, currently most of the renal tumors are being detected incidentally with their smaller size as a localized disease and, therefore, the need for adrenalectomy is questioned both in the presence of a normal appearing adrenal gland on preoperative radiological evaluation and as an intraoperative finding. Based on these, we investigated tumor related, pathological, and radiological factors that might affect adrenal involvement in patients with RCC.

I. Patient demographics and adrenal involvement

No association was detected between patient age, gender, and adrenal involvement by RCC in our study (Table 1) in accordance with other studies (8,9). Alamdari et al. suggested male gender as a risk factor for ipsilateral adrenal metastasis by RCC (10).

II. Tumor characteristics and adrenal involvement

Tumor localization in the kidney

It has been suggested that adrenal metastasis might be due to local invasion by continuous growth, particularly for the upper pole tumors, or by

hematogenous spread for mid and lower pole tumors (10,11). Therefore, tumors located in the upper pole of the kidney, which are anatomically closely related with the adrenal glands, were suggested to have an increased risk of adrenal metastasis (11,12). It is also suggested that, due to the presence of vessels that transverse the fibrous septum between the adrenal gland and the upper pole of the kidney providing a direct route for RCC cells, adrenal involvement is more commonly seen in upper pole kidney tumors (13). However, controversial reports exist in the literature. For example, although some studies failed to find an association between the location of the tumor in the kidney and adrenal involvement (8-10,14), others suggested that diffuse involvement of the kidney (8) or even a tendency towards lower pole tumors (15) as risk factors. In our study, 83.3% of the patients with upper pole kidney tumors had adrenal involvement, which did not reach the level of statistical significance (Table 1).

Tumor laterality

Due to common venous drainage of the upper pole of the left kidney with the adrenal gland, it was suggested that left sided kidney tumors have an increased risk for adrenal metastasis (9,16,17). In opposition to others who did not report an association (8,10), von Knobloch et al. reported even a higher percent of adrenal involvement for the right sided kidney tumors in a series of 589 patients (15). In our study, we did not find any relationship between tumor laterality and adrenal involvement (Table 1). Therefore, association of tumor laterality and adrenal involvement appear to be controversial.

Tumor size

Tumor size was found to be a significant risk factor for adrenal involvement in the literature (10). Siemer et al. recommended adrenalectomy in patients with a primary tumor >4 cm in size (8), whereas Paul et al. suggested adrenalectomy in greater than 8 cm sized tumors (9). However, others reported that correlation of tumor size and adrenal involvement was not statistically significant in their series including more than 500 cases (11,12). In our study, no association was detected between tumor size and adrenal metastases although patients with tumors >7 cm size have an increased rate of adrenal metastases, which was not significant ($P > 0.05$) (Table 1). Thus, debatable reports exist regarding tumor size and adrenal involvement in the literature.

Tumor multifocality

Although we did not evaluate the impact of number of tumors in the kidney (tumor multifocality) on adrenal involvement, controversial papers exist. Paul et al. failed to demonstrate the number of tumors as a risk factor of adrenal involvement in a series of 866 patients (9), whereas others reported that multifocal tumors in the kidney were associated with an increased risk of adrenal metastasis (11,18).

III. Radiologic features and adrenal involvement

Adrenal gland irregularity on CT

CT is an important radiologic modality in the evaluation of adrenal involvement by RCC. Detection of adrenal abnormalities, such as irregularity, enlarged diameter, mass lesion, nodule formation, heterogeneous density, non-visualization, and contiguous infiltration, should alert the urologist for possible adrenal metastasis. In our series, out of 6 patients with adrenal involvement, preoperative CT revealed adrenal irregularity in 4 patients and did not demonstrate any abnormality in the rest 2 patients although involvement by RCC was confirmed histopathologically. The presence of adrenal irregularity on CT was significantly associated with adrenal metastasis (Table 1). Therefore, CT demonstrates 66.7% sensitivity, 93.0% specificity, 57.1% positive predictive value, and 93.0% negative predictive value for detection of adrenal involvement in our study. Our results seems to be similar to the previously published series particularly having large number of patients (Table 3) (11,12,19). Tsui et al. reported that, in the presence of an adrenal mass, its size is a significant risk factor for adrenal involvement (11).

Apart from the abnormal appearance of the adrenal gland on CT, attenuation in non-contrast-enhanced slices (Hounsfield Unit, [HU]) might have an importance in the radiological evaluation of adrenal lesions (20). It was suggested that adrenal lesions <0 HU might be considered as benign, 0-15 HU probably benign, and >15 HU indeterminate lesions (20). On the other hand, magnetic resonance imaging (MRI) might also be useful and add more information to CT in the detection of adrenal metastasis particularly when CT is unreliable (21).

Atan et al. published a series of 198 patients with RCC, who were treated with RN and ipsilateral adrenalectomy including 5 different urology departments

Table 3. Comparison of published series concerning evaluation of adrenal glands by CT in patients with RCC in the literature. PPV: Positive predictive value, NPV: Negative predictive value.

Authors (Ref)	N	Sensitivity	Specificity	PPV	NPV
Moudouni et al. (12)	210	87%	97.7%	80%	98.4%
Tsui et al. (11)	511	99.6%	89.6%	92.8%	99.4%
Antonelli et al. (19)	1179	47%	99%	73%	96%
Our study	49	66.7%	93.0%	57.1%	93.0%

investigating the role of CT for detecting the number of tumors and adrenal gland involvement in patients with renal cell cancer (22). They reported that preoperative abnormal CT findings were less reliable for detecting tumor multifocality and adrenal gland involvement. Due to their histopathological evaluation, preoperative CT findings missed adrenal gland involvement and multifocal tumor in 4.7% and 4.3% of the patients, respectively. They concluded that although CT seems to be a reliable diagnostic tool for detecting adrenal gland involvement and tumor multifocality, more sophisticated radiological imaging methods or specific marker(s) are needed.

Presence of venous thrombosis on CT

Involvement of the renal vein by tumor thrombus has been suggested as a risk factor for adrenal involvement by several studies (11,12,23). Similarly, in our study, the presence of venous thrombosis was found to be significantly associated with adrenal involvement (Table 1). Tsui et al. reported that the risk of adrenal metastasis by RCC increased particularly in the presence of left renal vein thrombosis, which might be due to common venous drainage of the left adrenal and left kidney (11). However, Moudouni et al. found no significant correlation between left renal vein thrombus and adrenal involvement (12).

Presence of necrosis on CT

In our study, all of the patients with adrenal involvement were detected to have necrosis in their kidney tumors and the presence of necrosis was found to be a significant risk factor for adrenal metastasis (Table 1). To the best of our knowledge, our study is the first that investigates the impact of necrosis on adrenal involvement, which we think might be an important finding in the evaluation of kidney tumors.

IV. Histopathologic features and adrenal gland involvement by RCC

Histologic type

Tumor cell type was not found to be associated with adrenal involvement in our study (Table 2). All of the 6 patients with adrenal involvement had clear cell RCC in their kidneys. Siemer et al. also reported that tumor histology (cell type) did not affect adrenal metastasis in their series of 1635 patients (8).

Fuhrman grade

Currently, Fuhrman grading is the most frequently used histologic grading system in RCC, which is associated with local recurrence, pathologic stage, and survival (24). However, few studies have investigated the role of Fuhrman grade on adrenal gland involvement in the literature. In our study, increased Fuhrman grade was found to be significantly associated with adrenal gland involvement (Table 2). Ito et al. reported that, of the 12 patients with adrenal involvement by RCC, 3 had grade 3 (25%), 8 had grade 2 (67%), and 1 had (8%) disease in their series (25).

Capsular and perirenal fatty tissue invasion

Tumors extending to perirenal tissues, such as capsular and perirenal fat invasion (locally advanced disease), were considered as significant risk factors for adrenal involvement by RCC (10,19). Similarly, capsular and perirenal fatty tissue invasion were detected to be associated with ipsilateral adrenal involvement in our study (Table 2).

Vascular invasion

Although vascular invasion within the primary tumor was considered as an independent variable for predicting metastatic involvement of the adrenal gland by several

Table 4. Factors affecting adrenal gland involvement by RCC. RCC: Renal cell carcinoma, LN: Lymph node.

Significant risk factors for adrenal gland involvement by RCC	
1.	Adrenal gland irregularity on CT (P = 0.002)
2.	Presence of venous thrombosis on CT (P = 0.010)
3.	Presence of tumor necrosis on CT (P = 0.031)
4.	Presence of LN involvement by RCC (P = 0.013)
5.	Increased Fuhrman grade (P = 0.037)
6.	Presence of capsular invasion by RCC (P = 0.027)
7.	Presence of peripheral fat tissue invasion by RCC (P = 0.011)
Possible risk factors for adrenal gland involvement by RCC	
1.	Location of the tumor in the upper pole of the kidney (P = 0.077)
2.	Tumor size (P = 0.098)
3.	Vascular invasion (P = 0.067)
4.	Pathologic stage (P = 0.085)

studies (10,18), it was not found to be significantly associated with ipsilateral adrenal involvement, which might be due to the limited number of patients in the present study (Table 2).

Pathologic stage

Adrenal metastasis from primary RCC was found significantly more often in patients with advanced tumor stages by previous studies with larger number of patients (8,12,26,27). Tsui et al. reported that tumor stage correlated with the probability of adrenal spread, with T1-2, T3, and T4 tumors accounting for 0.6%, 7.8%, and 40% of cases, respectively (11). However, in our study no significant association was detected between tumor stage and adrenal involvement by RCC, which we think might be due to the limited number of patients with adrenal involvement in our study (Table 2).

A recent study demonstrated that tumors with adrenal gland invasion carry a worse prognosis than perinephric fat or renal vein invasion in patients with pT3 disease and they were found as an independent predictor of a patient's overall survival (28). Therefore, the

detection of adrenal gland involvement is very important in patients with RCC.

Presence of lymph node involvement

In accordance with the literature, presence of LN involvement was found to be significantly associated with adrenal involvement in our study (Table 2) (8,12,26,27).

Presence of metastasis

Although metastatic disease was not found to be associated with adrenal involvement in our study (Table 2), previous studies demonstrated that M+ disease was a risk factor for adrenal metastasis by RCC (8,9,12,18,26,27).

Conclusions

We recommend ipsilateral adrenalectomy with RN particularly in patients with increased tumor size, pathologic stage, localization of the tumor in the upper pole of the kidney, in the presence of adrenal gland irregularity/abnormality on CT scans, and with other possible risk factors (Table 4).

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