



# Associations Between Presenting Symptoms, Clinicopathological Parameters, and Prognosis in a Contemporary Series of Patients With Renal Cell Carcinoma

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**Purpose:** To evaluate the impact of presenting symptoms on survival in a contemporary series of patients with renal cell carcinoma (RCC).

**Materials and Methods:** We prospectively recorded data on the presenting symptoms, pathology, and RCC-specific survival of 633 consecutive RCC patients who underwent surgery between 2003 and 2012.

**Results:** Four hundred thirty-three RCCs (68%) were incidental, 111 (18%) were associated with local symptoms, and 89 (14%) were associated with systemic symptoms. Among those with incidental RCC, 317 patients (73%) were completely asymptomatic and 116 patients (27%) presented with symptoms not related to the tumor. During a median follow-up interval of 40 months (interquartile range: 39 to 69 months), 77 patients died from RCC. In univariate analyses, symptom classification was significantly associated with RCC-specific survival ( $p < 0.001$ ). Patients with incidental RCC and unrelated symptoms tended to have worse prognosis than did patients who were completely asymptomatic, although this difference was not statistically significant ( $p = 0.057$ ). The symptom classification was associated with advanced TNM stages ( $p < 0.001$ ) and grade ( $p < 0.001$ ).

**Conclusions:** This study confirms that presenting symptoms are associated with tumor characteristics and survival. The majority of RCCs are diagnosed incidentally in patients without any symptoms or with symptoms not related to RCC. Patients in the latter group tend to have a worse prognosis than do patients who are completely asymptomatic. With the increasing number of incidentally diagnosed RCCs, stratification of patients with incidental tumors may be prognostically relevant.

**Keywords:** *Diagnosis; Prognosis; Renal cell carcinoma; Symptoms*

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## INTRODUCTION

Historically, more than 90% of patients with renal cell carcinoma (RCC) present with symptoms and advanced stage disease [1-3]. With the widespread use of routine cross-sectional abdominal imaging, however, the landscape of patients presenting with RCC has changed dramatically. Although the incidence of RCC increased initially [4], a mi-

gration toward asymptomatic and early stages was observed [4,5], which ultimately led to better overall prognosis [6].

About 50% of patients present with symptoms related to a renal tumor [3,5], which in turn leads to the initiation of imaging or consultation with a urologist. The presence of symptoms is associated with more advanced tumor stages, metastatic disease, and an inverse prognosis [3,7-9].

Because this factor is available for all patients, it can be included in preoperative and postoperative prognostic assessment. It may therefore be relevant for urologists when planning therapy and surveillance. There are, however, few data on the proportion of asymptomatic or incidental and symptomatic cases among patients treated in the contemporary era of incidental renal tumors. Furthermore, the “incidentalness” of incidental tumors, i.e., the true indications and symptoms of these patients that led to imaging, are not well characterized. This may be significant for both urologists and nonurologic specialties.

The goals of this study were to assess the prevalence of presenting symptoms in a contemporary series and to evaluate associations with clinicopathological parameters and survival. Furthermore, with the identification of an increasing number of incidental renal tumors, we evaluated the true indications for imaging.

## MATERIALS AND METHODS

### 1. Study design and patient selection

Data on presenting symptoms, diagnostic imaging with referring medical specialty, treatment, pathology, and RCC-specific survival were prospectively collected in 633 consecutive RCC patients who were treated by partial or radical nephrectomy at Medical University of Vienna, Vienna, Austria between January 2003 and December 2012. The study was approved by the Medical University of Vienna.

### 2. Definitions and classification

Database variables were abstracted from patient charts and included age, gender, preoperative Eastern Cooperative Oncology Group Performance Status (ECOG PS); T, N, and M stage; Fuhrman grade; histological subtype; postoperative follow-up interval; date of death; cause of death; and date of recurrence. Symptoms were determined at the time of preoperative history and physical examination. Symptoms were classified according to Patard et al. [8] as follows: S1, asymptomatic/incidental tumor (S1a: totally asymptomatic, S1b: symptoms not related to renal tumor); S2, local symptoms; and S3, systemic symptoms. Weight loss was defined as an unintended decrease in weight of at least 5 pounds in 3 months. Paraneoplastic hypertension was defined as new onset of hypertension or worsening of preexisting hypertension [10].

Patients were staged according to the 2009 Tumor, Node, Metastasis criteria of the American Joint Committee on Cancer. Preoperative imaging included computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis and a conventional x-ray or CT of the chest. If patients were symptomatic for metastasis, additional imaging studies were undertaken, i.e., MRI of the liver, radionuclide bone scans, and CT or MRI of the brain. Nuclear grade was classified according to Fuhrman and subtype according to the World Health Organization

classification. Histological evaluation was performed by one specialized genitourinary pathologist (A.H.).

### 3. Statistical analysis

Categorical data are presented as numbers and proportions, and continuous data as median and interquartile range (IQR). Group differences in categorical and continuous variables were evaluated with chi-square tests and Wilcoxon rank sum tests or Kruskal-Wallis tests, respectively.

RCC-specific survival was calculated from the time of surgery to death from RCC or last follow-up, respectively. Cause of death was determined from death certificates, physician correspondence, or medical history. The Kaplan-Meier method was used to estimate survivor functions, which were compared with log-rank tests. Univariate Cox proportional hazards models were used to address the relative impact of categorically coded system classification and other clinical and pathological variables. To reduce the risk of over-fitting, only variables that were significantly associated with survival in the univariate analysis were included for multivariate modeling. All statistical testing was two-sided and a p-value < 0.05 was considered statistically significant. The statistical software STATA release 12 (StataCorp LP., College Station, TX, USA) was used for all analyses.

## RESULTS

### 1. Patient characteristics

Six hundred thirty-three consecutive patients with sporadic RCC were analyzed. The patients' median age at the time of surgery was 63 years (IQR, 54.3 to 72.2 years). A radical and partial nephrectomy was performed in 384 (61%) and 249 patients (39%), respectively. The most common histological subtype was clear cell (70%). One hundred patients (16%) presented with metastatic disease. The patient and tumor characteristics are summarized in Table 1.

### 2. Presenting symptoms

Four hundred and thirty-three patients (68%) were diagnosed with an incidental RCC (S1), of whom 317 patients (73%) were completely asymptomatic (S1a) and 116 patients (27%) presented with symptoms not related to the renal tumor (S1b). The indications for imaging in S1 cases are summarized in Table 2. S1a cases were most commonly diagnosed by routine ultrasound as part of a general health checkup (n=207, 33% of all cases) or by staging or follow-up of malignant tumors (n=74, 12% of all cases). S1b cases were most commonly diagnosed during workup of abdominal pain (n=38, 6% of all cases) or back pain (n=17, 3% of all cases).

Patients with local symptoms (S2; n=115, 18%) presented with flank pain (n=68, 11% of all cases), painless gross hematuria (n=62, 10% of all cases), or a palpable tumor (n=1, < 1%). Sixteen of these patients reported both

**TABLE 1.** Characteristics and prevalence of symptoms in a series of 633 consecutive RCC patients

Variable	Value
Age (y), median (IQR)	63 (54.3-72.2)
Gender	
Female	209 (33)
Male	424 (67)
ECOG PS	
0	397 (63)
≥ 1	236 (37)
Subtype	
Clear cell	446 (70)
Papillary	125 (20)
Chromophobe	53 (8)
Other	9 (2)
T stage	
pT1-T2	356 (56)
pT3-T4	277 (44)
N stage	
pN0/Nx	614 (97)
pN+	19 (3)
M stage	
M0	539 (85)
M1	94 (15)
Grade	
G1-G2	455 (72)
G3-G4	178 (28)
Symptom classification	
S1a	317 (50)
S1b	116 (18)
S2	111 (18)
S3	89 (14)

Values are presented as number (%) unless otherwise indicated. RCC, renal cell carcinoma; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

flank pain and gross hematuria (3% of all cases).

Tumors associated with systemic symptoms (S3; n=93, 15%) were most commonly symptomatic from bone or brain metastasis (n=46, 7% of all cases), weight loss (n=23, 4%), paraneoplastic hypertension (n=17, 3%), loss of energy (n=10, 2%), and fever (n=4, <1%).

The symptom classification was significantly associated with preoperative ECOG PS, T stage, N stage, M stage, and Fuhrman grade (all  $p < 0.01$ ) (Table 3). In a subgroup analysis, S1a and S1b were significantly associated with Fuhrman grade ( $p=0.025$ ), whereas no association was observed with ECOG PS, T stage, N stage, or M stage (Table 3). The proportion of patients presenting with a preoperative ECOG PS of 0 was 75% in S1a and 72% in S1b ( $p=0.53$ ) and decreased significantly to 48% in S2 and 24% in S3 ( $p < 0.001$ ).

### 3. Association with RCC-specific survival

During a median follow-up interval of 40 months (IQR, 39 to 69 months), 77 patients died from RCC. In univariate analyses, ECOG PS, T stage, N stage, M stage, Fuhrman

**TABLE 2.** Indications for imaging that led to diagnosis of 433 incidental renal tumors (group S1)

Group	Indications for imaging	No. (%)
S1a (n=317)	General health checkup	207 (65)
	Staging or follow-up of cancer	74 (23)
	Known asymptomatic renal cysts	8 (3)
	Aortic aneurysm	4 (1)
	Follow-up after solid organ transplantation	4 (1)
S1b (n=116)	Other	20 (7)
	Abdominal pain	38 (33)
	Back pain	17 (15)
	LUTS	15 (13)
	Diarrhea/vomiting	10 (9)
	Testicular pain	6 (5)
	Septicemia	5 (4)
	Vertigo	5 (4)
	Other	20 (17)

LUTS, lower urinary tract symptoms.

grade, and symptom classification were significantly associated with RCC-specific survival ( $p < 0.001$ ) (Table 4). In a subgroup analysis, a nonsignificant difference was noted between S1a and S1b ( $p=0.057$ ) (Fig. 1, Table 4). In the multivariate analysis, ECOG PS, T stage, N stage, M stage, and grade were independent prognostic factors (Table 4).

## DISCUSSION

We analyzed associations between presenting symptoms, pathology, and survival in a contemporary series of 633 consecutive RCC patients. We confirmed that presenting symptoms are associated with pathology and RCC-specific survival. At our institution, about 70% of RCCs were diagnosed incidentally. In our cohort, a nonsignificant trend toward a better prognosis for patients without any symptoms than for those presenting with symptoms not related to RCC was noted.

It has been shown that presenting symptoms are prognostically relevant in patients with RCC. This relationship is mainly based on the association of RCC with T stage and M stage, which are considered the most powerful prognostic factors [8,9]. Because the evidence suggests that the symptom classification adds prognostic information independent of these variables [3,7], stage does not entirely explain the relationship between presenting symptoms and prognosis.

In past decades, the proportion of incidental renal tumors has increased continuously as a result of the widespread use of routine cross-sectional abdominal imaging. The majority of these patients present either without any symptoms or with symptoms not related to RCC. Whereas only 7% to 13% of all RCCs were found incidentally in the 1960s [11,12], this proportion may now be as high as 80% [13]. However, there is considerable variability in recent research. For example, in the studies of Tsui et al. [14] and Sunela et al. [5], only 15% to 19% of renal tumors were diag-

**TABLE 3.** Associations of symptom classification with clinical and pathological variables of 633 patients with RCC

Variable	Symptom classification					
	S1a (n=317)	S1b (n=116)	p1	S2 (n=111)	S3 (n=89)	p2
ECOG PS			0.530			< 0.001
0	239 (60)	84 (21)		53 (14)	21 (5)	
≥1	78 (33)	32 (13)		58 (25)	68 (29)	
T stage			0.310			< 0.001
pT1-T2	208 (58)	70 (20)		52 (15)	26 (7)	
pT3-T4	109 (39)	46 (17)		59 (21)	63 (23)	
N stage			0.390			< 0.001
pN0/Nx	315 (51)	116 (19)		104 (17)	79 (13)	
pN+	2 (11)	0 (0)		7 (37)	10 (53)	
M stage			0.490			< 0.001
M0	303 (56)	109 (20)		93 (17)	34 (6)	
M1	14 (15)	7 (7)		18 (19)	55 (59)	
Grade			0.025			< 0.001
G1-G2	263 (58)	85 (19)		67 (15)	40 (9)	
G3-G4	54 (30)	31 (17)		44 (25)	49 (28)	
Subtype			0.490			0.054
Clear cell	214 (48)	79 (18)		77 (17)	76 (17)	
Papillary	72 (58)	22 (18)		25 (20)	6 (5)	
Chromophobe	28 (53)	12 (23)		8 (15)	5 (9)	
Other	3 (33)	3 (33)		1 (11)	2 (22)	

Values are presented as number (%).

P1 represents the p-values of chi-square tests for the groups S1a and S1b, p2 represents the p-values of chi-square tests between all 4 groups.

RCC, renal cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

nosed incidentally, whereas this proportion was 58% to 80% in other series [13,15]. Several explanations for these differences may exist. First, definitions and classifications of symptoms are somewhat general and are not standardized. This is specifically true for pain, which is multifactorial and can be related to many pathologic states. Differing judgment of symptoms and signs may lead to different symptom classification and thus in part account for the differing proportions of patients presenting with incidental tumors. For the current study, definitions from Kim et al. [10] and Patard et al. [8] were used. These definitions were a proposal for standardization and were adapted by the majority of recent studies.

Classification of symptoms remains subjective, however, and studies on symptom prevalence are difficult to compare. In addition, different referral patterns from primary to tertiary care centers may contribute to differing proportions of incidental renal tumors. Finally, health care systems differ considerably between countries. Because ultrasound studies are frequently performed in Austria and many patients are screened by ultrasound during general health checkups or while being treated for other medical conditions, more tumors are discovered incidentally, although ultrasound screening is not recommended in an unselected cohort [16,17].

The indications for imaging that have led to the detection of incidental renal tumors in contemporary series are not well documented. To our knowledge, only one such study

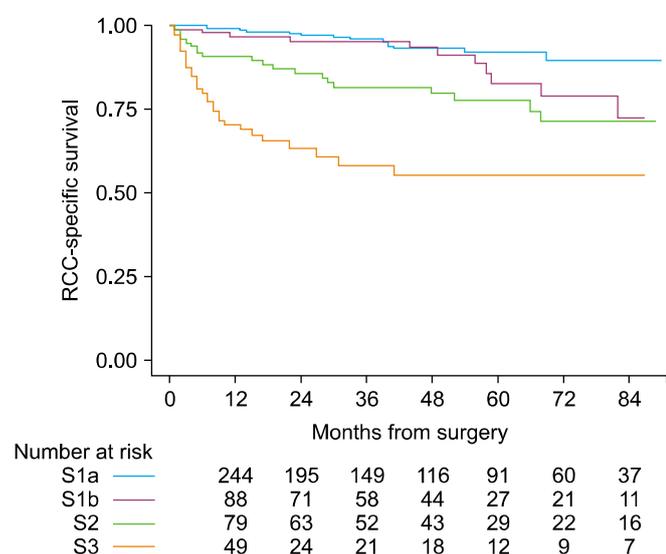
has been published in the literature. Sand et al. [18] reported that 33% of incidental renal tumors were found during staging or follow-up of other malignant diseases. Another 20% of tumors were discovered on imaging conducted because of signs or symptoms unrelated to RCC. The authors subdivided incidental renal tumors into categories of true and unrelated. In their study, the definitions differed considerably from the standard classification by Patard et al. [8]. Sand et al. [18] defined *true* incidental renal tumors as those discovered in patients with a known preexisting medical condition under surveillance and *unrelated* as those associated with symptoms that could not be classified as classic symptoms from RCC. The definition of unrelated incidental renal tumors is almost identical to the S1b group in the present study. In contrast with the true incidental renal tumors [18], the S1a group in the present study also included patients who were totally asymptomatic. Thus, our cohort covered patients with incidental renal tumors that were found during a general health checkup. In contrast with the case in Austria, in Norway, routine imaging in healthy subjects or patients with other medical conditions is rarely performed [18], which may explain this difference.

Our study confirms that presenting symptoms are associated with clinicopathological variables and are prognostically relevant. The symptom classification was significantly associated with ECOG PS, T stage, N stage, M stage, and Fuhrman grade. Interestingly, in the subgroup

**TABLE 4.** Univariate and multivariate Cox proportional hazard regression models for RCC-specific survival of 633 patients

Variable	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
ECOG PS ( $\geq 7$ vs. 0)	5.08	3.09-8.36	< 0.001	1.84	1.03-3.31	0.040
T stage (pT3/4 vs. pT1/2)	5.04	2.93-8.65	< 0.001	2.04	1.10-3.80	0.024
N stage (pN+ vs. pNx/N0)	10.83	5.81-20.19	< 0.001	2.07	1.07-4.04	0.031
M stage (M1 vs. M0)	22.14	13.31-36.80	< 0.001	10.80	5.84-19.97	< 0.001
Grade (G3/4 vs. G1/2)	5.05	3.16-8.06	< 0.001	1.96	1.15-3.36	0.013
Subtype	0.90	0.63-1.27	0.540	-	-	-
Symptom classification						
S1a	1.00			1.00		
S1b	2.13	0.98-4.63	0.057	1.97	0.90-4.31	0.090
S2	3.70	1.89-7.23	< 0.001	1.69	0.82-3.48	0.150
S3	9.84	5.27-18.36	< 0.001	1.29	0.62-2.70	0.490

RCC, renal cell carcinoma; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status.



**FIG. 1.** Kaplan-Meier specific survival according to Patard's symptom classification for 633 renal cell carcinoma (RCC) patients: S1, asymptomatic or incidental tumor (S1a, totally asymptomatic; S1b, symptoms not related to renal tumor); S2, local symptoms; and S3, systemic symptoms. S1b patients tended to have worse survival than did S1a patients, but this difference was not statistically significant.

analysis, we showed that Fuhrman grade was significantly lower in asymptomatic patients than in patients presenting with symptoms not related to disease (S1b). This relationship could bring new insights to our understanding of the role of tumor grade in presenting symptoms. In the Kaplan-Meier analysis, we found that patients with S1b tumors had worse survival than did those with S1a tumors, although this difference was not statistically significant. This may indicate that symptoms judged as not being related to RCC, such as abdominal pain and back pain, may have been in part due to RCC. Symptom classification was a significant prognostic factor in the univariate but not in

the multivariate analysis, which is possibly due to the strong association between symptoms and the presence of metastatic disease. In all, the role of incidental detection as an independent prognostic factor is not clear and considerable disagreement exists in the literature [3,8,19-21].

We analyzed both symptom classification and ECOG PS. Although there was a very high intercorrelation between both variables (Table 3) that may have impacted the multivariate statistical analysis, the variables measure different aspects in particular patients. Whereas the ECOG scale is a general measure of PS, the symptom classification is directly related to the disease. One may have an impaired PS due to concomitant comorbidity such as coronary heart disease or other malignancies and may be diagnosed with an incidental tumor (S1) [8]. Furthermore, it is possible that symptoms leading to the diagnosis of RCC do not impact PS. Because the ECOG PS is a dynamic variable and we analyzed only the preoperative ECOG PS, further research in this field is necessary.

Our study had several limitations. First, the study had a retrospective design although the data were collected prospectively. There was no standard for postoperative surveillance, which may have impacted the outcome measure and subsequent statistical evaluation. Furthermore, several additional prognostic factors, such as tumor necrosis, were not assessed. It was a single-center series, which introduces selection bias. Moreover, it is likely that this study was underpowered to detect a significant difference in the univariate analysis between the S1a and S1b groups, because the numbers of included patients and events were low. Correspondingly, we found no significant difference between all symptom groups in the multivariate analysis, although recent data have confirmed symptoms to be an independent prognostic factor [7-9]. Further prospective studies are necessary.

## CONCLUSIONS

This study confirms that presenting symptoms are associated with tumor characteristics and survival. Most RCCs are diagnosed incidentally without any symptoms or with symptoms not related to RCC. Patients in the latter group tend to have a worse prognosis than do patients who are completely asymptomatic. With an increasing number of incidentally diagnosed RCCs, substratification of patients with incidental tumors may be prognostically relevant.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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