Distant Metastasis of Renal Cell Carcinoma With a Diameter of 3 cm or Less—Which is Aggressive Cancer?

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Abbreviations and Acronyms

CT = computerized tomography

RCC = renal cell carcinoma

Submitted for publication October 28, 2009.

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Purpose: It was previously thought that renal cell carcinoma with a diameter of 3 cm or less has low potential to cause distant metastasis. However, metastasis develops in a small number of cases, which cannot be ignored. We investigated the clinicopathological characters of small renal cell carcinoma with metastasis to further understand this condition.

Materials and Methods: From January 1983 to February 2009, 165 cases of sporadic renal cell carcinoma 3 cm or less were treated at our department. Bilateral and von Hippel-Lindau disease were excluded from study. Clinicopathological parameters and outcome data were collected on each patient and analyzed.

Results: Histologically the 165 cases of primary renal cell carcinoma 3 cm or less included 151 of clear cell, 10 of papillary and 4 of chromophobe renal cell carcinoma, of which 4 had sarcomatoid differentiation, 6 had perinephric and/or sinus invasion and 20 had microvascular invasion. Overall we identified 10 metastatic cases (6.06%), of which 5 were synchronous. Univariate analysis revealed that age 60 years or greater ($p = 0.0139$), symptoms ($p = 0.0054$) and microvascular invasion ($p < 0.0001$) were significant risk factors. Multivariate analysis showed that only microvascular invasion was a significant risk factor ($p = 0.00062$). Perinephric and/or sinus fat invasion was not a significant risk factor.

Conclusions: Metastasis also develops in small renal cell carcinoma cases. Results suggest that microvascular invasion is a significant risk factor and patients with microvascular invasion should be followed more carefully.

Key Words: kidney; carcinoma, renal cell; neoplasm invasiveness; neoplasm metastasis; risk

SMALL RCC is reported to have a minimal potential of causing distant metastasis. Bell noted that only 1 of 38 patients with tumors less than 3 cm but 70 of 106 with tumors larger than 3 cm had metastasis.[1] Since then, many studies have shown that tumor size is an important risk factor for metastatic disease.[2,3] This holds true in the modern era[4–6] when many small RCCs are found incidentally by health evaluation on ultrasound and/or CT.[7,8]

In contrast, a few renal cancers with a small diameter have been reported to develop metastasis to other organs.[3,4,9–11] Several recent studies showed that even small renal cancers can have an increased incidence of high nuclear grade and tumor extension beyond the renal capsule, suggesting that they have aggressive potential.[12,13] Wunderlich et al reported distant metastasis in more than 10% of autopsy cases with a tumor diame-

0022-5347/10/1841-0064/0
THE JOURNAL OF UROLOGY®
© 2010 by AMERICAN UROLOGICAL ASSOCIATION EDUCATION AND RESEARCH, INC.
Vol. 184, 64-68, July 2010
Printed in U.S.A.
DOI:10.1016/j.juro.2010.03.019

ter of 20 mm or less.[12] Thus, it can be disputed whether renal tumors less than 3 cm should be treated as harmless, less aggressive disease.

However, currently the clinical and/or pathological characteristics, and risk factors of small RCC with metastasis have not been fully elucidated. Reports of these issues are lacking. We reviewed our RCC cases with metastasis to elucidate clinical and pathological aspects, and further understand this so-called harmless disease.

MATERIALS AND METHODS

From January 1983 to September 2008, 165 cases of sporadic RCC with a diameter of 3 cm or less were treated at our department. Bilateral or von Hippel-Lindau disease was excluded from study. All patients underwent preoperative and postoperative (every 1 to 6 months) evaluation, including routine blood test, chest x-ray and CT. Bone scintigraphy was done when indicated. We routinely perform chest x-ray every 3 months or chest CT every 6 months in the first 3 years and yearly thereafter to screen for metastatic disease. Charts were reviewed and the status of each patient was assessed by patient office visit and/or telephone call.

Histological stage, grade and subtype were assessed according to the Heidelberg classification and the 2002 American Joint Committee on Cancer version of the TNM staging system.[14,15] Microvascular invasion had been assessed routinely in cases of nephrectomy or partial nephrectomy upon diagnosis.

Statistical analysis was done using the log rank test for univariate analysis and Cox regression analysis for multivariate analysis. All statistical analysis was performed with StatMate II (ATMS, Tokyo, Japan).

RESULTS

RCC was confirmed histologically in all 127 males and 38 females with a median age of 59.0 years (range 23 to 83). A total of 94 left and 71 right tumors a median of 2.5 cm (range 0.6 to 3.0) were harvested. Radical and partial nephrectomy was performed for 81 renal tumors each. In the remaining 3 cases renal arterial embolization was done due to low performance status. In these cases RCC was confirmed histologically by biopsy of metastatic lesions and/or at autopsy. Histological diagnosis was made by biopsy of the metastatic lesion in only 1 case.

There were 151 clear cell, 10 papillary and 4 chromophobe RCCs, including 4 with sarcomatoid differentiation, 6 with extracapsular invasion (pT3a) and 1 with renal vein thrombus (pT3b). In 20 of 148 evaluable cases microvascular invasion was observed.

Five of 165 retrospectively evaluated cases of RCC 3 cm or less presented synchronously and in 5 metachronous metastasis developed at a median followup of 30.7 months (range 0.4 to 270.4) (table 1). In patients 1, 2 and 5 metastasis was confirmed

Table 1. *Clinical characteristics of men with RCC*

		Primary RCC						
Pt No.—Age	Chief Complaint	Side	Diameter (cm)	Stage	Histology	Microvascular Invasion	Metastatic Site (mos)	Outcome (mos)
					Synchronous			
1—71	Chest wall nodule	Rt	2.5	T1a	Clear cell	Yes	Bone	Bone metastasis (27)
2—70*	Rt arm pain	Rt	3.0	T1a	Clear cell, sarcomatoid component	Unknown	Bone	Ca death (5)
3—82*	Pubic pain	Lt	1.3	T1a	Clear cell, sarcomatoid component	Unknown	Bone	Ca death (6)
4—72	Lt hip joint pain	Lt	3.0	T1a	Clear cell, sarcomatoid component	Yes	Bone, lung	Ca death (17)
5—48*	Back pain	Rt	1.5	T1a	Clear cell, sarcomatoid component	Unknown	Bone	Ca death (27)
					Metachronous			
1—73	Gastric Ca followup	Rt	2.0	T1a	Clear cell	Yes	Lung (14)	Lung metastasis (17)
2—59	Regular medical evaluation	Lt	3.0	T1a	Clear cell	Yes	Lung (19)	Lung metastasis (19)
3—73	Myelodysplastic syndrome followup	Rt	2.3	T1a	Clear cell	No	Bone (17)	Myelodysplastic syndrome death (19)
4—60	Macroscopic hematuria	Lt	2.7	T3b	Clear cell	Yes	Lung (40), bone (48)	Ca death (68)
5—60	Regular medical evaluation	Rt	2.0	T1a	Clear cell	No	Bone (96)	Ca death (120)

* Embolization without nephrectomy.

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