Original Article

Renal cell carcinomas mass of <4 cm are not always indolent

Nessn H. Azawi[1,2], Lars Lund[2,3], Mikkel Fode[1]

[1]Department of Urology, Zealand University Hospital, Roskilde, [2]Clinical Institute of University of Southern Denmark, [3]Department of Urology, Odense University Hospital, Odense, Denmark

Abstract

Context: The rate of progression to metastatic disease in patients undergoing active surveillance for small renal tumors varies in the literature between 1% and 8%.

Aims: This study aims to examine the incidence of metastasis in small renal tumors of <4 cm in a Danish cohort.

Settings and Design: Retrospective.

Materials and Methods: Data on 106 patients who were diagnosed with renal cancer (RCC) of <4 cm by CT scan from January 2005 to December 2013 were collected retrospectively in January 2016 from patient charts and analyzed.

Statistical Analysis Used: The cancer-specific survival (CSS) and overall survival (OS) were estimated using Kaplan-Meier methods.

Results: The mean age was 62 years (range 40–84 years). Two patients (1.9%) had metastases at the time of diagnosis. Radical nephrectomy was performed in 74 patients (70%); of them, one patients (1.4%) experienced late metastasis (LM). Partial nephrectomy was performed in 30 patients (28%); of them, two patients (6.7%) experienced LM. The mean time to LM was 27 ± 12 months (95% confidence interval: 4–56). CSS rates were 98%, 97%, and 97% for 1, 3, and 5 years, respectively, while OS rates were 96%, 92%, and 86% for 1, 3, and 5 years, respectively. On multivariate analysis, tumor size ($P = 0.04$), pT3a ($P = 0.0017$), and patient's age ($P = 0.02$) at the time of diagnosis were significant predictors of LM.

Conclusions: Even small renal carcinomas may be aggressive, and caution should be taken when offering active surveillance.

Keywords: Partial nephrectomy, radical nephrectomy, recurrence, small renal masses, synchronized metastatic

Address for correspondence:
Dr. Nessn H. Azawi, Department of Urology, Zealand University Hospital, Urology, Sygehusvej 10, 4000 Roskilde, Denmark. E-mail: azawinessn@gmail.com
Received: 30.1.2017, **Accepted:** 12.04.2017

INTRODUCTION

The incidence of incidentally detected small (<4 cm) asymptomatic renal tumors have increased dramatically due to an increase in compute tomography (CT) scans for other indications.[1] This has prompted an increase in kidney surgeries, however, mortality from kidney cancer has not decreased, probably due to the fact that a large

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/UA.UA_18_17

How to cite this article: Azawi NH, Lund L, Fode M. Renal cell carcinomas mass of <4 cm are not always indolent. Urol Ann 2017;9:234-8.

proportion of these tumors are slow-growing/indolent.[2] Due to the potential morbidity associated with surgery, active surveillance (AS) may, therefore, be applied in elderly patients with severe comorbidities and small renal masses.[3] This conservative approach is recommended in selected patients in both European and Danish guidelines.[4] The rate of progression to metastatic disease in patients undergoing AS varies in the literature between 1% and 8%.[5,6]

The aim of our study was to examine the incidence of metastasis and to report cancer-specific survival (CSS) and overall survival (OS) in a Danish cohort of patients with renal cell carcinomas of <4 cm.

SUBJECTS AND METHODS

In January 2016, data were collected by chart review in patients who were diagnosed with renal tumors of <4 cm by CT scan and had a final pathological diagnosis of renal cell carcinoma at the Department of Urology, Zealand University Hospital, Roskilde from January 2005 to December 2013. Patient's characteristics were registered along with tumor size (TS) estimated by CT scan, histological cancer type, T-stage, Fuhrman grade, status of lymph node metastasis, necrosis, and status of surgical margins. We obtained permission for the study from the Danish Health and Medicines Authority in accordance with Danish legislation.

Pathological T-stage was assigned according to the 2009 tumor node metastasis classification.[7] Patients who underwent surgery before this time were reclassified accordingly by their histological features. N0 was assigned to patients with no evidence of clinical or pathological involvement of regional lymph nodes, and N1 was assigned when histological examination of the nephrectomy sample showed lymph nodes with malignant cells. Patients with clinical or pathological signs of metastasis at the time of diagnosis or surgery were defined as having primary metastasis (PM). Patients with clinical or pathological signs of metastasis detected more than 3 months after the diagnosis were defined as having late metastasis (LM). Tumors were classified into three groups according to TS; TS1 (0–20 mm), TS2 (>20–30 mm), and TS3 (>30–40 mm).

The duration of follow-up was defined as the period between the time of diagnosis and the last follow-up or death. To reduce bias in the attribution of the cause of death and to clearly distinguish between cancer-specific death and death from other causes, the cause of death was specifically confirmed in each deceased individual using the patient charts.

Statistical analysis

The CSS and OS were estimated using Kaplan–Meier methods. Differences in the survival probabilities by various histological and imagining features were tested by the log-rank test. Multivariable regression models were used to investigate tumor features associated with PM and LM with adjustment for TS, age, presence of sarcomatoid growth, necrosis, and lymph nodes involvement.

RESULTS

Data were obtained for 106 consecutive patients. The mean age at diagnosis was 62 years (range 40–84 years). The cohort consisted of 76 men (72%) and 30 women (28%). The mean follow-up period for all patients was 44 ± 22 months (95% confidence interval [CI]: 40–48). Two patients (1.9%) had metastases at the time of diagnosis; both have had pT1a tumor stage on the final histological report. The remaining 104 patients underwent surgery, but none of them received neoadjuvant therapy. Radical nephrectomy was performed in 74 patients (70%); of them, one patient (1.4%) diagnosed with pT3a tumor stage on the final histological report and experienced LM. Partial nephrectomy was performed in 30 patients (28%); of them two patients (6.7%) experienced LM; one of them diagnosed with pT1a and another one with pT3a on the final histological report. The LM rates did not differ significantly between surgical groups ($P = 0.41$). Overall, the LM rate was 2.9% within a mean follow-up period of 27 ± 12 months (95% CI: 4–56). The metastases were seen in the lung in one patient, in both lung and liver in another, and in bone and brain in the last patient. Three patients who underwent partial nephrectomy had positive surgical margins but none of them experienced LM. No local recurrences were detected in any patients. The distribution of pathological features and treatments in the whole cohort are shown in Table 1, while further characteristics of the patients with LM are descripted in Table 2.

Eleven patients (10.4%) died within the follow-up period. CSS rates were 98%, 97%, and 97% for 1, 3, and 5 years, respectively, while OS were 96%, 92%, and 86% for 1, 3, and 5 years, respectively [Figure 1a and b].

There was no significant difference in the 5 years CSS between patients with pT1a and pT3a tumors with rates of 98% and 92%, respectively ($P = 0.27$). Likewise, there was no difference in 5 years OS between pT1a and pT3a, with rates of 88% and 74%, respectively ($P = 0.65$) [Figure 1c and d].

Furthermore, there was no significant difference in neither 5 years CSS or 5 years OS between patients who underwent

Table 1: The distribution of the pathological feature and the kind of treatment

	T-size			Total, *n* (%)	*P*
	0-20, *n* (%)	>20-30, *n* (%)	>30-40, *n* (%)		
Fuhrman grade					
1	4 (3.77)	6 (5.66)	2 (1.89)	12 (11.32)	0.4261
2	15 (14.15)	28 (26.42)	28 (26.42)	71 (66.98)	
3	8 (7.55)	8 (7.55)	6 (5.66)	22 (20.75)	
4	0	1 (0.94)	0	1 (0.94)	
T-stage					
T1a	23 (21.70)	40 (37.74)	30 (28.30)	93 (87.74)	0.4133
T3a	4 (3.77)	3 (2.83)	6 (5.66)	13 (12.26)	
Histology					
Clear cell carcinoma	19 (17.92)	33 (31.13)	28 (26.42)	80 (75.47)	0.5008
Chromophobe	1 (0.94)	5 (4.72)	2 (1.89)	8 (7.55)	
Papillary	7 (6.60)	5 (4.72)	6 (5.66)	18 (16.98)	
Lymph nodes involvement					
No	26 (24.53)	42 (39.62)	35 (33.02)	103 (97.17)	1.0
Yes	1 (0.94)	1 (0.94)	1 (0.94)	3 (2.83)	
Primary metastasis					
No	27 (25.47)	42 (39.62)	35 (33.02)	104 (98.11)	1.0
Yes	0	1 (0.94)	1 (0.94)	2 (1.89)	
Late metastasis					
No	27 (25.96)	41 (39.42)	33 (31.73)	101 (97.12)	0.6166
Yes	0	1 (0.96)	2 (1.92)	3 (2.9)	
Treatment of the primary tumor					
No treatment	0	1 (0.94)	1 (0.94)	2 (1.89)	0.0191
Partial nephrectomy	12 (11.32)	13 (12.26)	4 (3.77)	29 (27.36)	
Radical nephrectomy	15 (14.15)	29 (27.36)	31 (29.25)	75 (70.75)	

$P<0.05$ considered significant

Table 2: The characteristic of the patients with metastasis disease

	Patient number	Died/ 5 years	Age	Time of survival or last follow-up	T-size	T-stage	Fuhrman grade	Necrosis	Sarcomatoid growth	Lymphovascular involvement	Treatment of the primary tumor
Primary	1	Yes	70	9	40	T1a	III	No	No	No	Radical nephrectomy
metastasis	2	Yes	50	18	30	T1a	II	No	No	No	Radical nephrectomy
Late	1	Yes	54	13	37	T3a	III	No	No	Yes	Radical nephrectomy
metastasis	2	No	49	45	35	T1a	II	No	No	No	Partial nephrectomy
	3	No	54	48	25	T3a	II	Yes	No	No	Partial nephrectomy

partial nephrectomy and radical nephrectomy, (96% vs. 97% (P = 0.94) for CSS and 82% versus 86% (P = 0.65) for OS [Figure 1e and f].

On multivariate analysis with adjustment for TS, T-stage, age, status of sarcomatoid growth, necrosis and lymph nodes status, TS (P = 0.04), pT3a (P = 0.0017) and patient's age at the time of diagnosis (P = 0.02) were significant predictors of LM.

DISCUSSION

In our study, we detected PM in 1.9% of patients with renal tumors of <4 cm. This is lower than reported in earlier cohorts,[8] which may be related to the fact that an increasing number of asymptomatic and indolent tumors are incidentally detected on CT scans performed for other indications.[1] Meanwhile, we found a 2.9% rate of LM in our cohort with an overall mean follow-up period of 44 months. In the literature, the rate of LM after surgery for localized and locally advanced renal cancer of <4 cm is reported to be about 4% with 10 years of follow-up.[9] As recurrences tend to develop within the first 5 years after primary surgery this is comparable to our findings.[10,11] Likewise, the 5 years CSS of 97% in our cohort is comparable to international reports,[9] indicating a good quality of oncological outcomes.

Interestingly, LM was found in 1.4% of patients who underwent radical nephrectomy and in 6.7% of patients who underwent partial nephrectomy. Although this is somewhat concerning and although a high proportion of LM after partial nephrectomy has been reported previously,[12] it is important to note that the difference in LM between different surgical techniques is not statistically significant (P = 0.41). In addition, CSS did not differ between the groups (P = 0.94), and partial nephrectomy was only performed in 28% of our patients. The relatively low proportion of partial nephrectomies is because the procedure was only introduced as a standard procedure in our department at the end of 2009.[13] It should be highlighted that partial nephrectomy is considered the gold

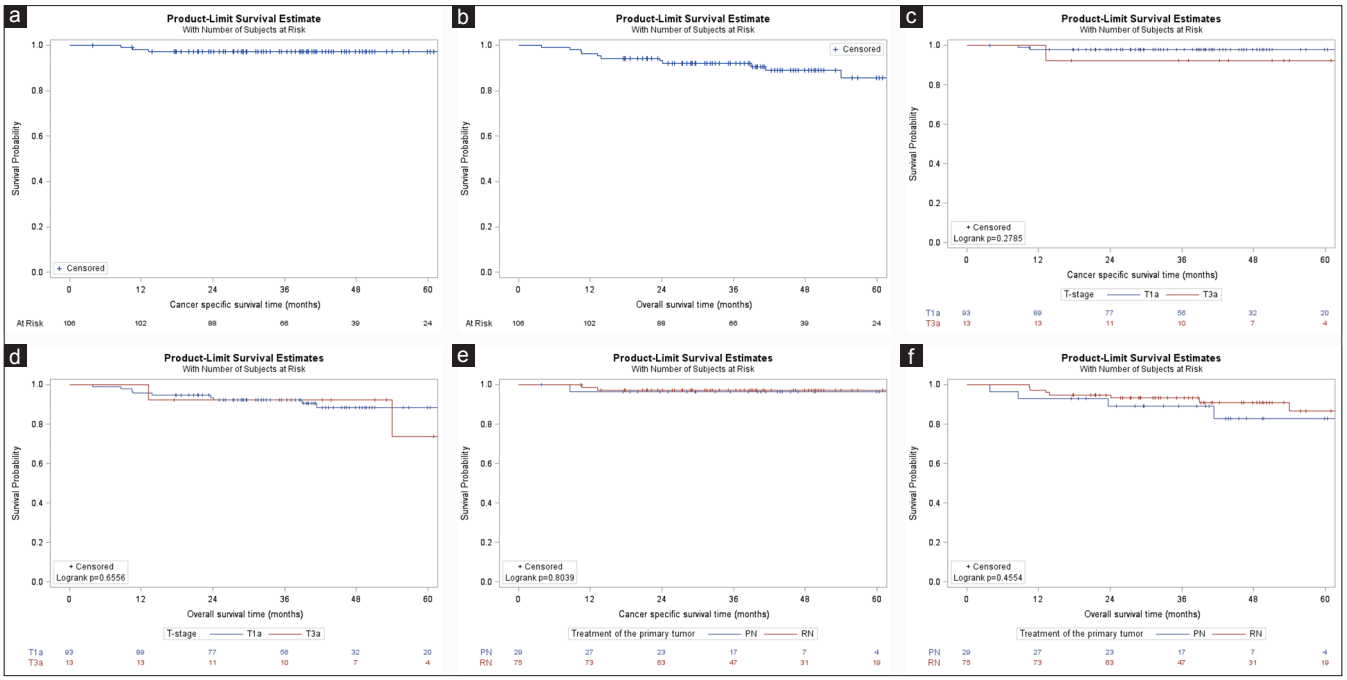

Figure 1: (a) Cancer-specific survival for patients with small renal cancer. (b) Overall survival for patients with small renal cancer. (c) Impact of T-stage on cancer specific survival. (d) Impact of T-stage on overall survival. (e) Impact of type of surgery on cancer specific survival. (f) Impact of type of surgery on overall survival

standard of treatment for small renal masses due to the high incidence of death due to cardiac disease associated with radical nephrectomy.[13]

Another important aspect of our data is that every diagnosis of tumor stage pT3a in our cohort, were due to the involvement of the renal hilum and that pT3 tumor was a significant predictor of developing LM on multivariate analysis. This means that the location of small tumor masses is an important predictor of LM and that renal hilum involvement may need to be factored in when deciding on follow-up programs following surgery.

As described in the introduction, individually tailored AS represents an alternative to surgery in the management of small renal masses.[14] However, metastatic renal carcinoma is associated with a poor prognosis[15,16] and as we detected such metastasis even following the surgical treatment of masses smaller than 4 cm, AS must be limited to patients with a short life expectancy. A broader applicability of AS may be possible in the future as genetic and biological studies show promise in determining the aggressive potential of renal lesions.[17,18] This may be used to guide treatment and to definitively recommend surgery or AS in a tumor-specific approach.

CONCLUSION

LM was detected in 2.9% of patients who underwent surgical treatment for renal cell carcinomas of <4 cm. This means that even small tumors may be aggressive and that caution should be taken when offering AS. New methods are needed to characterize the aggressiveness of renal masses to offer the optimal management.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. JAMA 1999;281:1628-31.
2. 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.
3. Jewett MA, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, *et al.* Active surveillance of small renal masses: Progression patterns of early stage kidney cancer. Eur Urol 2011;60:39-44.
4. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, *et al.* EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67:913-24.
5. Chawla SN, Crispen PL, Hanlon AL, Greenberg RE, Chen DY, Uzzo RG. The natural history of observed enhancing renal masses: Meta-analysis and review of the world literature. J Urol 2006;175:425-31.
6. Remzi M, Ozsoy M, Klingler HC, Susani M, Waldert M, Seitz C, *et al.* Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. J Urol 2006;176:896-9.
7. Sobin LH, Compton CC. TNM seventh edition: What's new, what's changed: Communication from the International Union Against Cancer and the American Joint Committee on Cancer. Cancer 2010;116:5336-9.

8. Lughezzani G, Jeldres C, Isbarn H, Perrotte P, Shariat SF, Sun M, *et al*. Tumor size is a determinant of the rate of stage T1 renal cell cancer synchronous metastasis. J Urol 2009;182:1287-93.
9. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. J Urol 2000;163:442-5.
10. Breda A, Konijeti R, Lam JS. Patterns of recurrence and surveillance strategies for renal cell carcinoma following surgical resection. Expert Rev Anticancer Ther 2007;7:847-62.
11. Ljungberg B, Alamdari FI, Rasmuson T, Roos G. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. BJU Int 1999;84:405-11.
12. Lee H, Lee JK, Kim K, Kwak C, Kim HH, Byun SS, *et al*. Risk of metastasis for T1a renal cell carcinoma. World J Urol 2016;34:553-9.
13. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC, *et al*. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. J Urol 2008;179:468-71.
14. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DY, *et al*. Small renal masses progressing to metastases under active surveillance: A systematic review and pooled analysis. Cancer 2012;118:997-1006.
15. Miyao N, Naito S, Ozono S, Shinohara N, Masumori N, Igarashi T, *et al*. Late recurrence of renal cell carcinoma: Retrospective and collaborative study of the Japanese Society of Renal Cancer. Urology 2011;77:379-84.
16. Kubackova K, Melichar B, Bortlicek Z, Pavlik T, Poprach A, Svoboda M, *et al*. Comparison of two prognostic models in patients with metastatic renal cancer treated with sunitinib: A retrospective, registry-based study. Target Oncol 2015;10:557-63.
17. Chen F, Zhang Y, Senbabaoglu Y, Ciriello G, Yang L, Reznik E, *et al*. Multilevel genomics-based taxonomy of renal cell carcinoma. Cell Rep 2016;14:2476-89.
18. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, *et al*. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer 2005;104:2084-91.