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

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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

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

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proportion of these tumors are slow-growing/indolent.[5]
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.[4] 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%.[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 described 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
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

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

| Fuhrman grade | T-size 0-20, n (%) | >20-30, n (%) | >30-40, n (%) | Total, n (%) | P |
|---------------|-------------------|---------------|---------------|--------------|---|
| 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 | Fuhrman grade | T-size 0-20, n (%) | >20-30, n (%) | >30-40, n (%) | Total, n (%) | P |
|---------|---------------|-------------------|---------------|---------------|--------------|---|
| 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 | T‑size 0-20, n (%) | >20-30, n (%) | >30-40, n (%) | Total, n (%) | P |
|-----------|-------------------|---------------|---------------|--------------|---|
| 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 | T‑size 0-20, n (%) | >20-30, n (%) | >30-40, n (%) | Total, n (%) | P |
|-------------------------|-------------------|---------------|---------------|--------------|---|
| 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      | T‑size 0-20, n (%) | >20-30, n (%) | >30-40, n (%) | Total, n (%) | P |
|-------------------------|-------------------|---------------|---------------|--------------|---|
| 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         | T‑size 0-20, n (%) | >20-30, n (%) | >30-40, n (%) | Total, n (%) | P |
|-------------------------|-------------------|---------------|---------------|--------------|---|
| 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)      |   |

**Table 2: The characteristic of the patients with metastasis disease**

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

P<0.05 considered significant.

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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.

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**Conflicts of interest**

There are no conflicts of interest.

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