Recurrence rates and survival in a Danish cohort with renal cell carcinoma

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ABSTRACT

INTRODUCTION: Patients with localised and locally advanced renal cancer experience about 20% recurrence during a five-year follow-up period. The aim of the present study was to report recurrence rates and survival in a Danish population with renal cancer.

METHODS: Data on patients diagnosed with renal cell carcinoma (RCC) at our institute from January 2005 to December 2013 were collected retrospectively.

RESULTS: Overall, 367 patients were diagnosed with RCC during the period, and 78 patients (21%) presented with metastasis. The mean follow-up period for all patients was 41 months (standard deviation = 29, 95% confidence interval: 38-44). The total recurrence rates (RRs) at one, three and five years were 4.5%, 13.5% and 22.3%, respectively. Overall survival rates in the patients who underwent surgery with localised and locally advanced disease were 96.1%, 88.2% and 78.3% for one, three and five years, respectively. The mean time to first recurrence was 26.6 months. The one-year RR was 1.2%, 5.5% and 13.8% for low, intermediate and high-risk Leibovich scores, respectively. The three-year RR was 8.3%, 14.1% and 29.6% for low, intermediate and high-risk Leibovich scores, respectively; and the five-year RR was 12.0%, 26.6% and 52.9% for low, intermediate and high-risk Leibovich scores, respectively.

CONCLUSIONS: RRs after localised and locally advanced RCC was 22%. According to the risk of recurrence, we recommend a follow-up programme after nephrectomy with computed tomography every second year for low-risk patients, annually for intermediate-risk patients and every six months for high-risk patients.

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Renal cell carcinoma (RCC) is associated with a significantly higher annual mortality-to-incidence ratio than any other common urological malignancies [1]. About 20-30% of all patients have metastatic disease at the time of diagnosis [2-4]. In addition, about 20% of the patients who undergo nephrectomy with a curative intent have been shown to develop metastatic RCC (mRCC) during follow-up [5, 6]. In most cases, recurrence will develop within the first five years after primary surgery [7, 8]. Metastatic renal cancer is associated with a poor prognosis, and early treatment of the metastasis may improve the survival rate [9, 10].

The aim of the present study was to report recurrence rate (RR) following surgery for localised or locally advanced disease and to report cancer-specific survival (CSS) and overall survival (OS) in a Danish population with renal cancer.

METHODS

Data on patients diagnosed with RCC at the Department of Urology, Roskilde Hospital, Denmark, from January 2005 to December 2013 were collected retrospectively from patient charts and analysed. We obtained permission from the Danish Health and Medicines Authority. All patients had undergone a computed tomography (CT)-urography as well as either a thoracic X-ray or CT as part of their diagnostic work-up.

Clinical T-stage was assigned according to the 2009 TNM classification [11]. Patients who underwent surgery before this time were re-classified 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. M0 was assigned to patients with no evidence of clinical or pathological distant metastasis, and M1 was assigned to patients with evidence of clinical or pathological metastasis. None of the patients received neoadjuvant treatment in conjunction with surgery.

Recurrence was defined as tumour relapse in the operative field, regional lymph nodes and/or distant metastasis as diagnosed either by a CT or histologically by biopsies or local resections of metastases. Surgical resection status was defined as positive when the tumour was described as not radically resected and as negative when the tumour was removed radically.

The duration of follow-up was defined as the period from diagnosis to last follow-up or death. Data collection was performed in January 2015. In order to reduce bias in the attribution of cause of death and to clearly distinguish between disease-specific death and death from other causes, the cause of death was specifically assessed in each deceased individual using the patient charts.

ORIGINAL ARTICLE

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TABLE 1

The demographic distribution of the data in the patients with localized and locally advanced disease.

Age, mean (± SD) [95% CI], yrs	64 (± 10) [63-65]
Histological classification, n (%)	
RCC	229 (79.2)
Papillary	40 (13.9)
Chromophobe	15 (5.2)
Frequency missing	5 (1.7)
Total	289
Pathological tumour stage, n (%)	
T1a	97 (33.5)
T1b	66 (22.8)
T2a-T2b	52 (17.9)
T3-T4	69 (23.8)
Frequency missing	5 (1.3)
Total	289
Tumour size, n (%)	
≤ 4 cm	111 (38.4)
> 4-7 cm	91 (31.5)
> 7-10 cm	48 (16.6)
> 10 cm	39 (13.5)
Total	289
Fuhrman grade, n (%)	
Low grade (I-II)	85 (29.4)
High grade (III-IV)	127 (43.9)
Frequency missing	77 (26.6)
Total	289
Leibovich score, n (%)	
Low risk (0-2)	163 (56.4)
Intermediate risk (3-5)	74 (25.6)
High risk (> 5)	52 (17.9)
Total	289
Necrosis, n (%)	
No necrosis	130 (44.9)
Necrosis	159 (55.0)
Total	289
Sarcomatoid, n (%)	
Not sarcomatoid	277 (95.8)
Sarcomatoid	12 (4.1)
Total	289
Lymph nodes, n (%)	
Lymph nodes-positive	10 (3.4)
Lymph nodes-negative	279 (96.5)
Total	289
Surgical resection status, n (%)	
Negative resection	276 (95.5)
Positive resection	13 (4.4)
Total	289
Number of sites of recurrence, n (%)	
1	27 (51.9)
2	18 (34.6)
3	3 (5.7)
≥ 4	4 (7.6)
Total	52
Year of diagnosis, n (%)	
2005-2007	59 (20.4)
2008-2010	90 (31.2)
2011-2013	139 (48.1)
Frequency missing	1 (0.3)
Total	289
Treatment of recurrences, n (%)	
No treatment	3 (5.7)
Oncological	27 (51.9)
Surgical	22 (42.4)
Total	52

CI = confidence interval; RCC = renal cell carcinoma; SD = standard deviation.

Statistical methods

The RR, CSS and OS were estimated using Kaplan-Meier methods. For estimation of RR, patients who were recurrence-free at their last date of follow-up or at death were censored. Differences in the RR and survival probabilities by various histological features were tested by the log-rank test. The multivariable Cox proportional hazards ratio (HR) was used to investigate tumour features associated with RR, OS and CSS with adjustment for age, Leibovich score, presence of sarcomatoid growth or metastasis and positive surgical resection.

Trial registration: none.

RESULTS

Overall, 367 patients were diagnosed with RCC during the period, and 78 patients (21%) had metastases at the time of diagnosis. The remaining 289 patients presented with local or locally advanced renal cancer. The mean age was 64 years (range: 37-88 years). Males represented 238 patients (65%), and females represented 129 patients (35%).

Radical nephrectomy was performed in 269 patients (73.3%, including debulking surgery in 39 patients with metastasis), while partial nephrectomy was performed in 59 patients (16.1%). A total of 23 patients (6.3%) received oncological treatment only and information about the primary treatment was missing for 16 patients (4.4%). A group of 55 patients (15%) died within the first 12 months after diagnosis. The mean follow-up period for all patients was 41 months (standard deviation (SD) = 29, 95% confidence interval (CI): 38-44). A total of 52 patients experienced late metastasis within five years. Demographic data are shown in **Table 1**.

Univariate analysis

Recurrence rates

RR was calculated in the 289 patients who underwent surgery for localised or locally advanced disease. The total RRs at one, three, and five years were 4.5%, 13% and 22%, respectively. The mean time to first recurrence was 26.6 months (SD = 20, 95% CI: 20.9-32.1). Advanced T-stage was a significant predictor of recurrence with HR 13.5 (standard error (SE) = 0.6, 95% CI: 4.1-44.8, p < 0.0001), HR = 7.1 (SE = 0.63, 95% CI: 2.1-25.1, p = 0.002), and HR = 3.9 (SE = 0.67, CI: 1.04-14.9, p = 0.04) for T-stage (T3-T4), T2 stage (T2a-T2b), and T1b compared with stage T1a, respectively. A high Fuhrman grade (III-IV) was a significant predictor of recurrence compared with a low Fuhrman grade (I-II) with a HR = 2.1 (SE = 0.32, 95% CI: 1.2-4.2, p = 0.16). Presence of sarcomatoid growth and necrosis were significant predictors of recurrences, with HR = 5.7 (SE = 0.44, 95% CI: 2.4-13.8, p < 0.0001), and HR = 3.0 (SE = 0.29, 95% CI: 1.7-5.5, p = 0.0001), respectively. A tumour size between 7 and 10 cm and more than 10 cm were significant poor predictors of recurrence compared with a tumour size of less than 4 cm, HR = 3 (SE = 0.42, 95% CI: 1.4-7, p = 0.005) and HR = 4.6 (SE = 0.42, 95% CI: 2.0-10.5, p = 0.0003), respectively. Presence of metastasis to the lymph nodes (N1) and positive surgical margins were also significant predictors of recurrences, HR = 4.9 (SE = 0.4, 95% CI: 2.1-11.6, p = 0.0002) and HR = 5 (SE = 0.3, 95% CI: 2.3-10.8, p < 0.0001), respectively. Patients with high- and intermediate-risk Leibovich scores had significantly higher RRs than patients with a low-risk Leibovich score, HR = 5.7 (SE = 0.33, 95% CI: 2.9-10.9, p < 0.0001) and HR = 2.2 (SE = 0.36, 95% CI: 1-4.5, p = 0.027), respectively.

One-year RRs were 1.2%, 5.5% and 13.8% for low, intermediate and high-risk Leibovich scores, respectively. Three-year RRs were 8.3%, 14.1% and 29.6% for low, intermediate and high-risk Leibovich scores, respectively, and five-year RRs were 12%, 26.6% and 52.9% for low, intermediate and high-risk Leibovich scores, respectively (**Figure 1**).

Overall survival

OS rates in patients who underwent surgery for localised and locally advanced disease were 96.1%, 88.2% and 78.3% for one, three and five years, respectively.

The OS rates for all patients with renal cancer were 85%, 75% and 66% for one, three and five years, respectively (**Figure 2**). Primary metastatic disease and late metastasis were signs of a poor prognosis. The OS rates for patients with primary metastasis were 42%, 26% and 18% for one, three and five years, respectively; and 94%, 71% 44% for patients with late metastasis. Primary metastasis increased the risk of dying by HR = 16.4 (SE = 0.23, 95% CI: 10.2-26.6, p < 0.0001), while late metastasis increased the risk of dying by HR = 4.7 (SE = 0.24, 95% CI: 2.7-8.1, p < 0.0001).

Advanced T-stage tumours (T3-T4) increased the risk of dying by HR = 4 (SE = 0.32, 95% CI: 2-7.4, p < 0.0001) compared with T1 tumour stage. A high Fuhrman grade, a tumour size of more than 10 cm, presence of sarcomatoid growth, positive lymph nodes and positive surgical margins all increase the risk of dying by HR = 2.4 (SE = 0.28, 95% CI: 1.4-4.1, p = 0.0016), HR = 2 (SE = 0.25, 95% CI: 1.2-3.2, p = 0.006), HR = 2.3 (SE = 0.29, 95% CI: 1.3-4.2, p = 0.003), HR = 3.4 (SE = 0.23, 95% CI: 2.1-5.4, p < 0.0001) and HR = 2.3 (SE = 0.33, 95% CI: 1.2-4.4, p = 0.01), respectively.

FIGURE 1

Impact of Leibovich scores on recurrence rate.

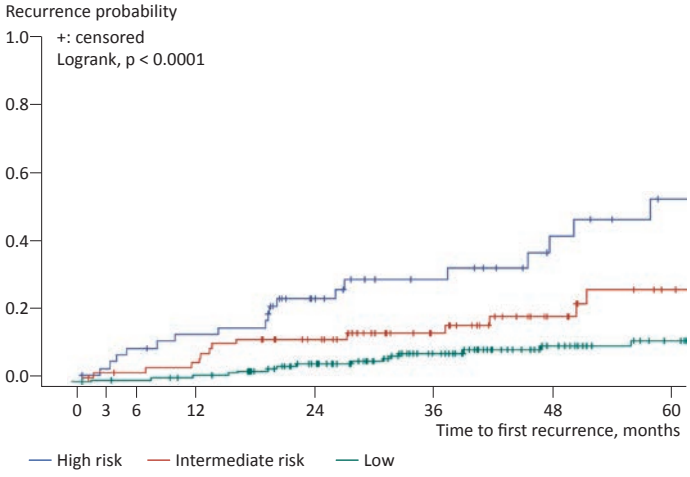
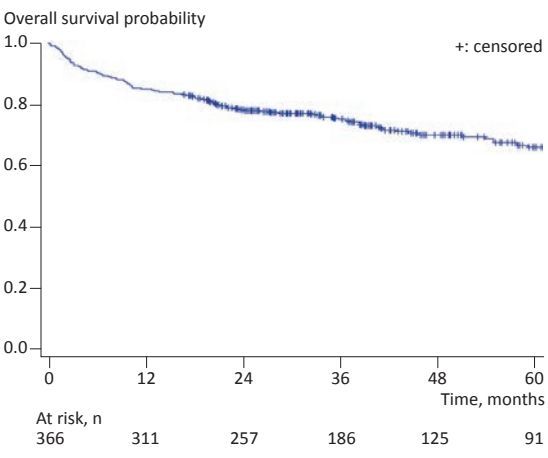


FIGURE 2



Overall survival for patients with renal cell carcinoma.

TABLE 2

Differences in the cancer-specific survival probabilities by various histological features tested by the log-rank test.

	Estimate (standard error) [p-value[a]]	Hazard ratio (95% confidence limits)
Metastasis		
Non-metastasis	Reference	
Late metastasis	2.5 (0.4) [< 0.0001]	13.2 (5.9-29.7)
Primary metastasis	3.6 (0.4) [< 0.0001]	40.4 (18.8-86.7)
T-stage		
T1a	Reference	
T1b	0.3 (0.7) [0.6616]	1.3 (0.3-5.4)
T2a-T2b	1.2 (0.5) [0.0319]	3.5 (1.1-11.3)
T3-T4	2.2 (0.5) [< 0.0001]	9.4 (3.3-26.6)
Fuhrman grade		
Low	Reference	
High	1.1 (0.3) [0.0017]	3.1 (1.5-6.3)
Tumour size		
≤ 4 cm	Reference	
> 4-7 cm	0.1 (0.3) [0.7988]	0.9 (0.5-1.7)
> 7-10 cm	0.4 (0.3) [0.2241]	1.4 (0.7-2.7)
> 10 cm	0.9 (0.3) [0.0030]	2.5 (1.3-4.5)
Sarcoma		
No sarcoma	Reference	
Sarcoma	0.9 (0.3) [0.0056]	2.6 (1.3-5.0)
Lymph nodes		
Lymph nodes negative	Reference	
Lymph nodes positive	1.1 (0.3) [< 0.0001]	3.2 (1.8-5.6)
Necrosis		
No necrosis	Reference	
Necrosis	0.3 (0.2) [0.2158]	1.3 (0.8-2.0)
Surgical resection		
Surgical resection negative	Reference	
Surgical resection positive	0.8 (0.4) [0.0349]	2.3 (1.0-5.0)

a) p < 0.05 considered significant.

TABLE 3

Multivariate analysis on recurrence rate, overall survival, and cancer-specific survival with control for patients' age, Leibovich risk, metastasis status, sarcoma, and surgical resection status.

	Estimate (standard error) [p-value[a]]	Hazard ratio (95% confidence limits)
Recurrence rate		
Age	0.01 (0.01) [0.4568]	1.0 (0.9-1.0)
Leibovich risk	0.6 (0.1) [< 0.0001]	1.9 (1.4-2.7)
Sarcoma	1.5 (0.4) [0.0011]	4.5 (1.8-11.4)
Surgical resection	1.2 (0.4) [0.0034]	3.3 (1.4-7.5)
Overall survival		
Age	0.02 (0.01) [0.0071]	1.0 (1.0-1.0)
Sarcoma	0.6 (0.3) [0.0505]	1.8 (0.9-3.3)
Surgical resection	0.3 (0.3) [0.2918]	1.4 (0.7-2.9)
Metastatic status	0.7 (0.1) [< 0.0001]	2.1 (1.7-2.7)
Cancer-specific survival		
Age	0.02 (0.01199) [0.0204]	1.0 (1.0-1.0)
Sarcoma	0.5 (0.35134) [0.1066]	1.7 (0.8-3.5)
Surgical resection	0.2 (0.42832) [0.6153]	1.2 (0.5-2.8)
Metastatic status	1.02 (0.13534) [< 0.0001]	2.7 (2.1-3.6)

a) p < 0.05 considered significant.

Cancer-specific survival

The CSS in patients who underwent surgery for localised and locally advanced disease were 99.3%, 99.3 and 98.9% for one, three and five years, respectively.

The CSS rates for all patients with renal cancer were 88%, 82% and 74% for one, three and five years, respectively. Metastatic disease and late metastasis were signs of a poor CSS. CSS rates for patients with primary metastasis were 47%, 36% and 31% for one, three and five years, respectively; and 96%, 74% and 46% for patients with late metastasis. The impact of other features is described in **Table 2**.

Multivariate analysis

Leibovich score (p < 0.0001), presence of sarcomatoid growth (p = 0.0011) and the status of surgical margins (p = 0.0034) were all significant, independent predictors of recurrence, while patients' age at the time of diagnosis was not. Age (p = 0.007), presence of sarcomatoid growth (p = 0.51) and metastasis (p < 0.0001) continued to be significant and independent predictors of a poor OS, while age (p = 0.0204) and status of metastasis (p < 0.0001) were the only significant and independent predictors of a poor CSS (**Table 3**).

DISCUSSION

We reported Danish data on renal cancer patients and investigated the RR, OS and CSS. RR increased, while OS and CSS decreased with advanced pathological features in both univariate and multivariate analyses. This trend has been described before [12].

In our cohort, the RRs within five years following surgery for non-metastatic renal cancer was 22%. This rate is comparable to the international reports, where the RRs in the past two decades decreased from 30% to 20% [5, 6]. This may be owed to the early detection of renal tumours as well as to the proper treatment of renal cancer patients in our institution. The CSS of 98.9% that we observed at five-year follow-up for localised and locally advanced disease was higher than reported in the literature, which may be owed to considerable development in the surgical and anesthesiological techniques in the past decade [13].

Patients in the high Leibovich risk group had RRs of 52.9% at five years. For comparison, a study from 1999 reported a five-year RR of 93% in such patients [8]. This difference can likely be attributed to the improvements in treatment, which have been developed over the past few decades.

Metastatic disease at first presentation was present in 78 patients (21%) of 367 patients in this study, which is comparable to recent studies [2-4]. This relatively low proportion may be owed to early detection of renal cancer because of the increase in the use of CT.

In total, three- and five-year OS rates for all patients with RCC regardless of treatment modality were 75% and 66%, respectively, which is comparable to international reports. OS deteriorated when patients had metastasis at the time of diagnosis or later. This is also in accordance with the existing literature [14].

The number of patients diagnosed with small renal tumours and low-risk disease according to the Leibovich score represented half of the cohort. The RRs for these patients were significantly lower than in the intermediate and high-risk cohorts. The increased number of incidental detection of small renal tumours is associated with increased use of CT in the past decade [2-4, 15].

The Leibovich risk score system is used to stratify the risk of recurrence according to histological features, and the system was validated externally in many studies [15-18] . Therefore, follow-up after renal cancer surgery is guided by the Leibovich risk system in Denmark. Because the survival of patients may improve with early detection and treatment of recurrences, we believe that the goal is to check for recurrence in patients with a risk of 5% or more. In order to achieve this, we recommend that patients with a low Leibovich risk receive follow-up every second year, while the cohort with intermediate Leibovich risk receive follow-up annually. Patients with a high Leibovich risk should undergo follow-up every six months (see Figure 1). As we only investigated the RR within the five-year period following diagnosis, our recommendation is limited to this time period. Other studies have reported the on RR after renal cancer even later, up to ten years [13].

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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