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European Association of Urology

Platinum Priority – Kidney Cancer

Editorial by Eric C. Umbreit and R. Houston Thompson on pp. 983–985 of this issue

Metastatic Potential in Renal Cell Carcinomas ≤7 cm: Swedish Kidney Cancer Quality Register Data

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Article info

Article history:
Accepted June 9, 2011
Published online ahead of print on July 1, 2011

Keywords:
Renal cell carcinoma
Tumor size
Tumor category
Lymph node metastases
Distant metastases

Abstract

Background: Renal cell carcinoma (RCC) represents 2–3% of all malignancies and accounts for approximately 90% of all kidney malignancies. An increasing proportion of RCCs are discovered incidentally, and the average tumor diameter at diagnosis has decreased over the last few decades. Small RCCs have often been regarded by many as relatively harmless.
Objective: The objective was to evaluate the incidence of local T-category distribution and lymph node and distant metastases in relation to tumor size in RCCs ≤7 cm in a nationally based patient population.
Design, setting, and participants: Data were extracted from the National Swedish Kidney Cancer Register containing 3489 RCCs diagnosed between 2005 and 2008. This is a population-based registry including 99% of all RCCs diagnosed nationwide. The study included 2033 patients having a tumor ≤7 cm in diameter.
Measurements: The size of the tumors was compared with sex, age, cause of diagnosis, Fuhrman grade, RCC type, and TNM category.
Results and limitations: Most RCCs were discovered incidentally and incidence correlated inversely to tumor size. There were 887 (43%) patients with category T1a tumors, 836 (40%) with category T1b, 174 (8%) with T3a, 131 (6%) with T3b/c, and 12 (1%) patients had invasion of adjacent organs (T4). A total of 309 (15%) patients had lymph node and/or distant metastases. Of the 177 1- to 2-cm RCCs, category T3 tumors were identified in three patients and lymph node and/or distant metastases were identified in 8 (5%). Only for tumors ≤1 cm was there neither advanced stage nor metastasis. The occurrence of locally advanced growth, lymph node and distant metastases, and high tumor grade correlated to tumor size. Patients with Fuhrman grade III or IV had a four-fold greater risk of metastases than grades I or II.
Conclusions: Lymph node and distant metastases occur even in small RCCs. Risk of metastases increases with tumor size. The data clearly show that small RCCs also have a malignant potential and should be properly evaluated and adequately treated.

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1. Introduction

Renal cell carcinoma (RCC) represents 2–3% of all malignancies, having the highest incidence in industrialized countries [1]. RCC is the most common kidney malignancy, comprising different tumor types with specific histopathologic and genetic characteristics [2]. In 2006, 63 300 new cases and 26 400 RCC-related deaths were estimated within the

0302-2838/$ – see back matter doi:10.1016/j.eururo.2011.06.029

European Union [3]. Over recent decades, an annual incidence increase of approximately 2% has been observed worldwide, although in some European countries (eg, Denmark and Sweden) a decrease in incidence was found during the last decade. The overall mortality rate increased in Europe until the 1990s; thereafter, stabilizing or declining mortality rates have been observed in some Western European countries [4,5].

Due to an increased use of continuously improved imaging techniques, there has been a shift toward an increased detection of symptomless tumors over the years. The number of incidentally detected RCCs has increased substantially and presently represents the largest group of detected RCCs. These tumors are generally smaller and have a lower category compared to symptomatic RCCs [6]. In general, many clinicians have regarded the small RCCs ($\leq$4 cm diameter) as having a benign biologic behavior [7,8]. However, some authors have reported the occurrence of adverse factors in small RCCs, including invasion of the renal capsule, tumor thrombus, and lymph node and distant metastasis [9,10]. Most published patient materials have been compiled from secondary centers, indicating selected populations.

In the present study on RCCs $\leq$7 cm, we analyzed the occurrence of adverse factors based on the National Swedish Kidney Cancer Quality Register (NSKCR). The size of the tumors was compared with sex, age, cause of diagnosis, Fuhrman grade, RCC type, and TNM category.

2. Materials and methods

2.1. Patients

Since 2005, all diagnosed RCCs from the six health care regions in Sweden are reported to the NSKCR and the obligatory national cancer register for all malignancies. The data for the NSKCR are reported by the clinicians that diagnose RCC by any method. By 2008 the register contained 3489 tumors, which covered 99% of the kidney cancer cases in Sweden during that period. The register contains information on tumor characteristics such as RCC type, nuclear grade, tumor size, and TNM classification according to the Union for International Cancer Control 2002 [11]. Histopathologic classification of grade was performed according to Fuhrman and RCC type according to the World Health Organization [12,13]. In 42 patients with >1 tumor (86 tumors total), the largest tumor defined the tumor stage. Tumor size was measured by computed tomography (CT) or magnetic resonance imaging (MRI). Node evaluation was based on CT and/or MRI examinations of the abdomen or findings at surgery. The classification N0 was dependent on a performed negative CT of the abdomen and without palpable enlarged lymph nodes at surgery. CT of the thorax was mandatory to rule out pulmonary metastases; patients were registered as MX if they did not have a preoperative CT of the thorax. CT of the thorax was performed in 67% of these patients; this percentage increased during the registration period. Pulmonary x-ray was routinely done in the remaining patients. Patients with metastasis demonstrated by any method were registered as M1, patients without signs or symptoms of metastasis and investigated with CT or MRI of the abdomen and CT of the thorax were defined as M0.

The present study includes 2033 patients having 2076 tumors $\leq$7 cm. There were 1212 males and 821 females with a mean age of 67 yr (median age: 68; range: 14–92 yr). Data on histopathologic variables were available from 1917 patients (1953 tumors) and unavailable for 116 patients who had no surgery or biopsy performed. Radical or partial nephrectomy was performed in 1801 patients and 39 received cryotherapy or radiofrequency treatment. In 26 of these 39 patients, both surgery and minimal invasive therapy were used. For 193 patients (9%), no active treatment of the primary tumor was registered. Pathologic T category was used for the 1801 patients who had surgery, while clinical T category only was used for the remaining 232 patients.

We reviewed patients' files and retrospectively validated reports from approximately 300 patients of the register, including all category T4 RCCs, all RCCs < 2 cm with any risk factor for progress, all patients with missing tumor size, and all tumors where any discrepancy was noted between tumor stage and size. In this validation process we found discrepancies that were corrected in the register in 108 patients in this cohort, including 25 patients with missing data on tumor size.

2.2. Statistics

Statistics in this paper are mainly descriptive. Absolute numbers are shown in figures. Probability of occurrence of lymph node and distant metastases is shown with point estimation and 95% confidence interval (CI). Cuzick's Wilcoxon-type test for trend and the chi-square test were used for statistical analysis. P values < 0.05 were considered statistically significant. All analyses were performed with Stata/IC v.10.1 (StataCorp, College Station, TX, USA).

3. Results

The proportion of patients with incidentally diagnosed RCCs correlated inversely with tumor size ($p < 0.001$), as illustrated in Figure 1. No difference in incidental diagnosis was found between genders. Younger women had a significantly lower proportion of RCCs than men ($p < 0.001$). This difference in gender distribution was not found with increased age (Fig. 2). The distribution of T category relative to tumor size is given in Table 1. The register contained complete data on tumor size and T category for 98% of tumors. Three of 164 patients (2%) with 1- to 2-cm RCCs had invasion of the perirenal and/or renal sinus fat, or tumor thrombus formations ($\geq$pT3). The local aggressive features of the tumors increased significantly ($p < 0.001$) with increasing tumor size. Tumors measuring 6–7 cm had advanced local tumor extension ($\geq$pT3) in 34% of patients.

Distribution data of RCC type relative to tumor size, available for 1917 tumors, is shown in Table 2. Overall, clear-cell RCC accounted for 80% of tumors, with significantly increasing proportion by tumor size ($p = 0.002$). The frequency of papillary and chromophobe RCCs was highest in small tumors, with a decreased occurrence by increasing tumor size. Collecting-duct carcinoma was uncommon, found only in tumors >3 cm.

Fuhrman grade was registered in 1725 (90%) of the 1917 tumors with any histologic information available. The proportion of low-grade tumors (grade I-II) decreased and the occurrence of high-grade tumors (grades III-IV) increased by tumor size (Fig. 3).

The proportion of occurrence with lymph node and distant metastases increased with tumor size, as shown in Figure 4. Of RCCs with a diameter of 6–7 cm, 32% had metastases. In Table 3, the proportion of advanced

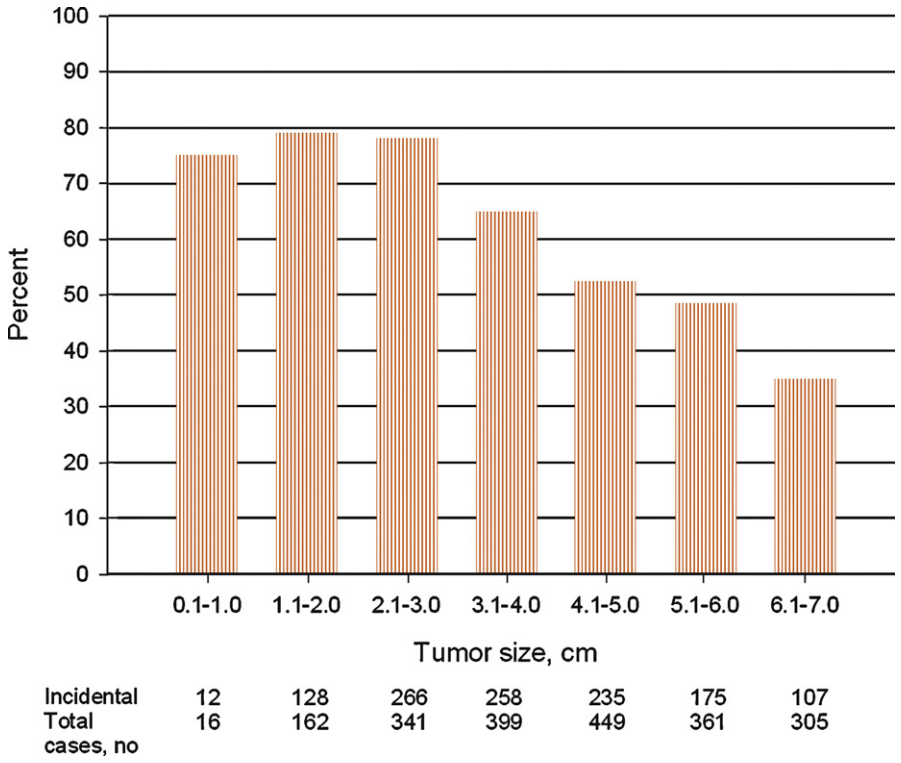

Fig. 1 – Proportion of incidentally detected renal cell carcinoma (RCC) in relation to tumor size in 2033 patients with RCC. The numbers under each column show incidentally detected patients as well as total number of patients.

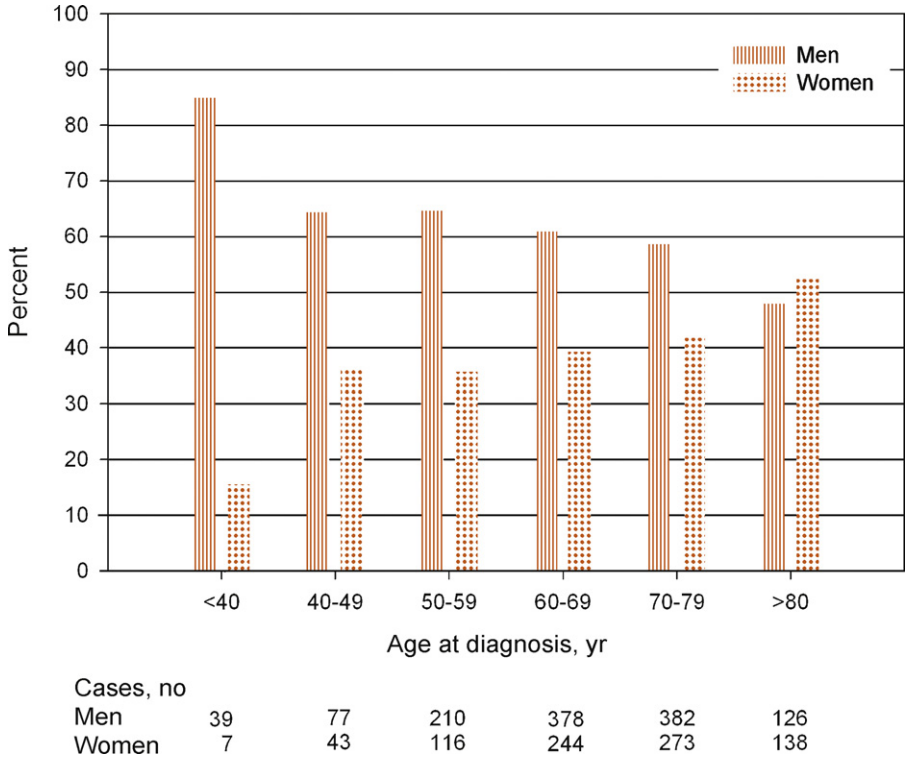

Fig. 2 – Distribution of gender and age in 2033 patients with renal cell carcinoma. The numbers below show the distribution of genders relative to tumor size.

Table 1 – Distribution of T category relative to tumor size in 2033 patients with renal cell carcinoma ≤7 cm*

Size, cm	T1		T3a		T3b-c		T4		TX		Missing		Total
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
0.1–1.0	16	100	0	0	0	0	0	0	0	0	0	0	16
1.1–2.0	157	97	2	1	1	1	0	0	2	1	0	0	162
2.1–3.0	322	94	13	4	2	1	0	0	4	1	0	0	341
3.1–4.0	362	91	22	6	9	2	2	1	4	1	0	0	399
4.1–5.0	369	82	44	10	23	5	4	1	9	2	0	0	449
5.1–6.0	263	73	47	13	39	11	2	1	8	2	2	1	361
6.1–7.0	197	65	44	14	55	18	4	1	4	1	1	0	305
Total	1686	83	172	8	129	6	12	1	31	2	3	0	2033

* Patients registered as TX and those with missing data are shown.

Table 2 – Relationship between renal cell carcinoma (RCC) type and tumor size in 1917 patients having tumors with available histopathology*

Size, cm	RCC type												
	Clear cell		Papillary		Chromophobe		Collecting duct		Unclassified		Missing		Total
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
0.1–1.0	8	53	5	33	2	13	0	–	0	–	0	–	15
1.1–2.0	108	71	33	22	8	5	0	–	3	2	0	–	152
2.1–3.0	258	79	45	14	17	5	0	–	7	2	1	0.3	328
3.1–4.0	298	79	44	12	20	5	2	0.5	12	3	1	0.3	377
4.1–5.0	340	81	40	10	18	4	1	0.2	19	5	0	–	418
5.1–6.0	279	81	36	11	16	5	2	0.6	10	3	0	–	343
6.1–7.0	234	82	25	9	8	3	2	0.7	12	4	3	1	284
Total	1525	80	228	12	89	5	7	0.4	63	3	5	0.3	1917

* Unclassified or other RCC types ($n = 63$) and missing data on RCC type ($n = 5$) in the register are included.

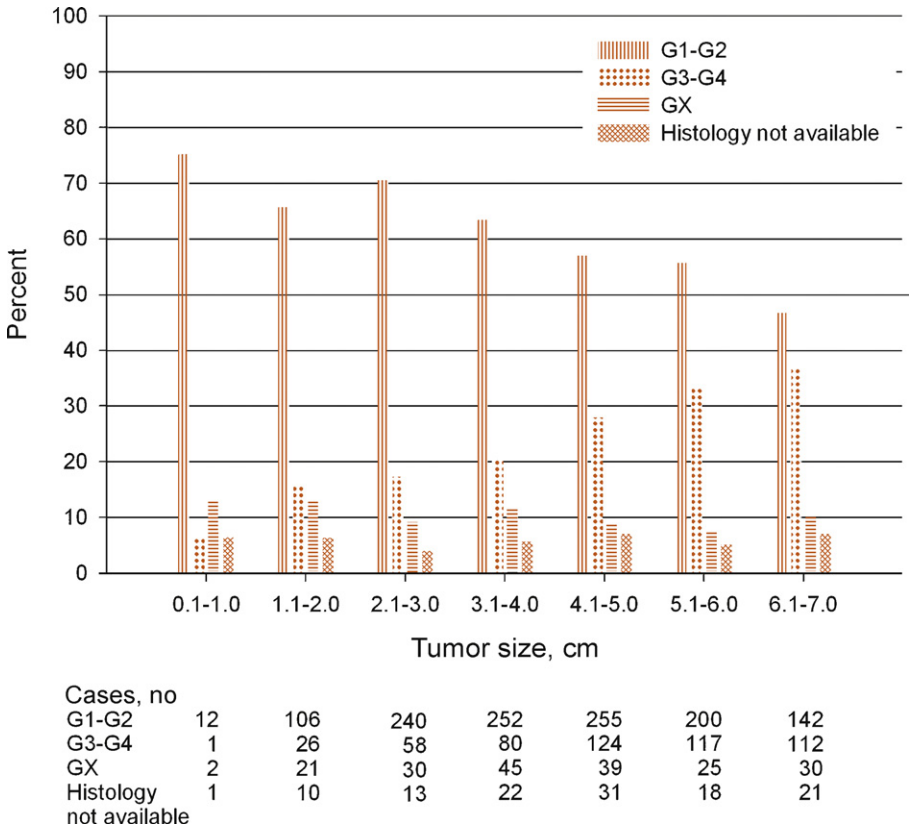

Fig. 3 – Distribution of Fuhrman high-grade (G3-G4) and low-grade (G1-G2) tumors relative to tumor size in 1725 patients with registered grade. Tumors reported as GX ($n = 192$) and those patients without reported histopathologic grade ($n = 116$) are included.

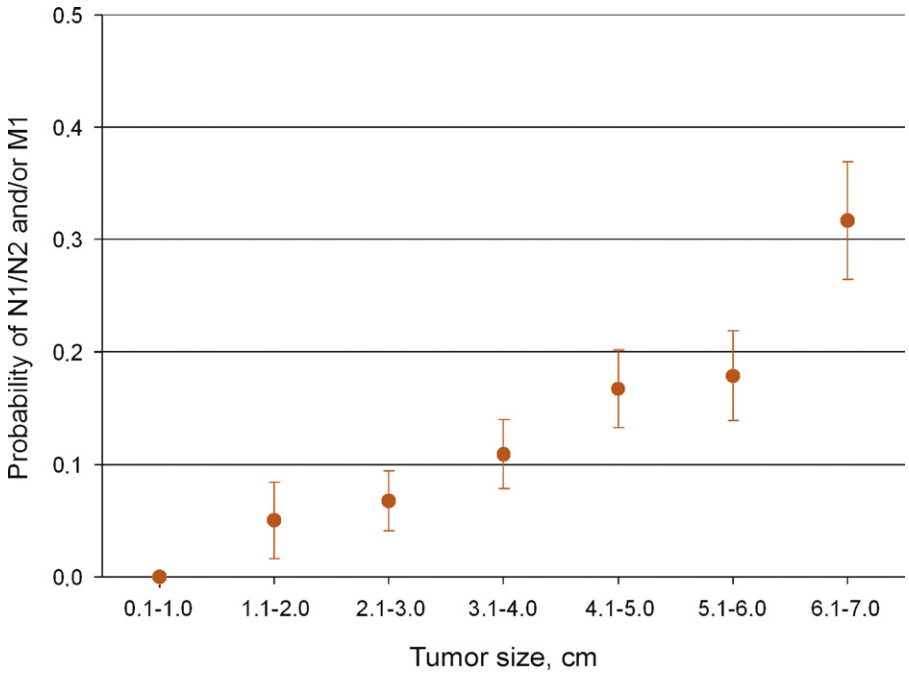

Fig. 4 – Occurrence of lymph node and/or distant metastases relative to tumor size in 2018 patients with renal cell carcinoma. The dashed lines show upper and lower limits of the 95% confidence interval. Fifteen patients (0.7%) with missing data on N or M category were excluded.

T category, the occurrence of lymph node and distant metastases, and high Fuhrman grade in relation to tumor size are presented. Using any of these risk factors for disease progression in an individual patient, 41% of patients with RCCs >7 cm have a significant risk for an adverse clinical course. This combined risk increased significantly with tumor size ($p = 0.002$), from 6% in RCCs 0–1 cm to a 64% risk in patients with 6- to 7-cm tumors. Among 218 patients with metastatic disease and available histology, 77% of tumors were clear cell, 8% papillary, 1% chromophobe, and 13% were unclassified RCC (Table 4). There was no difference between clear cell, papillary, or chromophobe RCCs, while unclassified RCC more often had lymph node metastases ($p < 0.001$) compared with the other RCC types. Clear cell RCCs had more frequent ($p = 0.023$) distant metastases than chromophobe RCCs, and unclassified RCC more frequently had distant metastases ($p < 0.001$) compared with the other RCC types (Table 4).

4. Discussion

The study shows that small RCCs have an aggressive potential, resulting in lymph node and distal metastases even in a 1- to 2-cm tumor. In this first report from the NSKCR, we present data on RCC in a nationwide cohort. The register included 99% of all RCCs diagnosed. We have validated a large number of the cases by reviewing the patient files, but still this study has limitations inherent to the nature of the register. Information on clinical, radiologic, and histopathologic data has been gathered from all Swedish hospitals, which might have included interpretation discrepancy. A discrepancy might, in part, also be possible due to an individual clinician's interpretation of clinical results. However, the data registration has been performed prospectively and the data are continuously validated at the registration centers, reducing the likelihood of aberrant data. The greatest strength of this registry is that

Table 3 – Distribution of poor prognostic factors in relation to tumor size for 2033 patients with renal cell carcinoma

Size, cm	Risk factors for poor prognosis										Total
	T3-T4		N1-N2		M1		G3-G4		Any risk factor		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
0.1–1.0	0	0	0	0	0	0	1	6	1	6	16
1.1–2.0	3	2	4	2	7	4	25	15	33	20	162
2.1–3.0	15	4	9	3	18	5	58	17	79	23	341
3.1–4.0	33	8	17	4	39	10	80	20	129	32	399
4.1–5.0	71	16	35	8	64	14	124	28	199	44	449
5.1–6.0	88	24	23	6	55	15	118	33	192	53	361
6.1–7.0	103	34	43	14	84	28	112	37	195	64	305
Total	313	15	131	6	267	13	518	25	828	41	2033

Table 4 – The occurrence of lymph node and distant metastasis grouped according to renal cell carcinoma type and relative to tumor size in 1917 patients with available histolopathologic information

Size, cm	Clear cell						Papillary						Chromophobe						Other/unclassified						Total	
	N1-N2		M1		Total		N1-N2		M1		Total		N1-N2		M1		Total		N1-N2		M1		Total			
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
0.1–1.0	0	–	0	–	8	100	0	–	0	–	5	100	0	–	0	–	2	100	0	–	0	–	0	–	15	100
1.1–2.0	1	0.9	2	1.9	108	100	0	–	2	6.1	33	100	0	–	0	–	8	100	1	33.3	2	66.7	3	100	152	100
2.1–3.0	6	2.3	12	4.7	258	100	1	2.2	3	6.7	45	100	0	–	0	–	17	100	2	25.0	1	12.5	8	100	328	100
3.1–4.0	5	1.7	19	6.4	298	100	3	6.8	4	9.1	44	100	0	–	1	5.0	20	100	2	13.3	5	33.3	15	100	377	100
4.1–5.0	19	5.6	42	12.4	340	100	4	10.0	3	7.5	40	100	1	5.6	1	5.6	18	100	4	20.0	7	35.0	20	100	418	100
5.1–6.0	10	3.6	38	13.6	279	100	2	5.6	4	11.1	36	100	2	12.5	0	–	16	100	3	25.0	4	33.3	12	100	343	100
6.1–7.0	21	9.0	55	23.5	234	100	2	8.0	2	8.0	25	100	1	12.5	1	12.5	8	100	12	70.6	10	58.8	17	100	284	100
Total	62	4.1	168	11.0	1525	100	12	5.3	18	7.9	228	100	4	4.5	3	3.4	89	100	24	32.0	29	38.7	75	100	1917	100

it is performed nationwide, thereby including nearly all RCCs diagnosed in Sweden during the study period and including patients with their local standard of care, therefore minimizing selection bias.

The distribution of RCC type showed a similar trend, as previously presented in another population-based cohort [14]. The proportion of papillary and chromophobe RCCs in the present study were inversely correlated to tumor size, having the highest representation in the smallest tumors. The proportion of clear cell RCCs was more frequent with increasing size, which is consistent with previous studies [9,14]. We found that 78% of tumors <3 cm were discovered incidentally. RCCs >5 cm in our cohort were diagnosed, in a majority of patients, due to symptoms. This correlates well with the trend that RCCs diagnosed in recent decades have smaller average tumor size and an increasing proportion of the RCCs have been discovered incidentally [6]. Among patients under age 40, only 15% were women, while in older patients the distribution was even between the genders. One possible explanation might be an increased incidental detection by, for example, trauma CT in men, although the reason for the uneven distribution in younger patients is unknown.

Our study shows that even T1a RCCs have lymph node and distal metastases in a relatively high proportion. We found that 11% of 3- to 4-cm tumors, the upper limit for T1a tumors, had either lymph node or distant metastases. In total, 7% of all RCCs <4 cm had distant metastases. Only in tumors <1 cm were neither lymph node nor distant metastases observed. Our data support previous reports from referral centers showing similar findings in proportion of metastases and increased occurrence by tumor size [10,15]. The 10% of patients with distant metastasis in 3- to 4-cm RCCs in our study was greater than that of Remzi and Pahernik, who found, respectively, 8% and 6% of RCCs with distant metastases in their studies [10,15]. Our higher proportion might be explained by our nationwide population-based inclusion, but might also be due, in some cases, to misinterpretation or incorrect coding in the register. Patients with nonmetastatic smaller tumors suitable for surgery might be overrepresented at referral centers, lowering the proportion of metastases compared with nationwide data. In a recent publication from the US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database, 7% of metastatic disease was reported in 3- to 4-cm tumors [16]. The authors further reported distant metastases in 4% of 1- to 2-cm tumors and in 18% of 6- to 7-cm tumors, supporting our data. Furthermore, in an institutional study, Kunkle et al. [17] estimated the probability for synchronous metastases by logistic regression. According to their data, patients with a 4-cm RCC would be expected to have an 18% probability of metastatic disease, and tumor size significantly predicted synchronous metastatic disease [17]. We found a continuous increase in occurrence of metastases by tumor size, which is in contrast to the findings of Klatte et al, who reported that tumor size did not predict synchronous metastatic disease [18].

In the present study, a similar size-dependent incidence of locally aggressive T category (pT3-pT4) was found. For patients with 1- to 2-cm RCCs, 2% had locally aggressive growth increasing to 34% for 6- to 7-cm RCCs. The occurrence of 8% pT3-T4 category RCCs in our register for 3- to 4-cm tumors is relatively low compared with 36% in the study of Remzi and 12% in Pathernik's study [10,15]. This difference in incidence may reflect the fact that our data are population based, while their studies were based on referral patients who probably had locally more advanced tumors.

Although low histopathologic grade predominated in RCCs $\leq$7 cm, high-grade RCCs increased with tumor size. This proportion was slightly higher than that reported in the SEER cohort, but comparable with that of Remzi et al. [15]. By combining occurrence of T3-T4, N1-2, M1, and high-grade tumors, which are negative predictive factors in RCC, we observed a 20% combined risk for adverse outcome in 1- to 2-cm tumors increasing to a 64% risk for patients with RCC between 6 and 7 cm. These data indicate that small RCCs have a high potential for metastatic disease.

The risk for tumor spread is an obvious concern in the clinical management of RCC. Van Poppel and Joniau reviewed the natural history and biologic potential of small renal masses to evaluate whether surveillance was an option for their treatment [19]. They found that tumor size alone did not provide adequate information for deciding on the optimal treatment and the preoperative evaluation should be thorough. Although tumor size correlates with metastatic occurrence, it is obvious that small RCCs are not always harmless. Treatment algorithms and experimental treatments should consider that all RCCs are potentially deadly despite size [17,20]. Our results show that all RCCs should be thoroughly evaluated and adequately treated as recommended by the European Association of Urology guidelines [21].

5. Conclusions

Our study shows that lymph node and distant metastases occur even in small RCCs. This risk of metastases increases with tumor size. By combining data on histologic grade and local and distant tumor spread, small RCCs demonstrate high malignancy potential.

Author contributions: Börje Ljungberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ljungberg, Lundstam.
Acquisition of data: Lundstam, Guðmundsson, Erikson, Ljungberg.
Analysis and interpretation of data: Hellborg, Guðmundsson, Ljungberg, Hellborg.
Drafting of the manuscript: Guðmundsson, Lundstam, Ljungberg.
Critical revision of the manuscript for important intellectual content: Ljungberg, Lundstam, Erikson, Hellborg.
Statistical analysis: Hellborg.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Ljungberg, Lundstam.
Other (specify): None.

Financial disclosures: I certify that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Acknowledgment statement: The authors acknowledge the assistance of Michael Haney for linguistic revision of the manuscript and the Swedish kidney cancer quality register group.

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