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No improvement in renal cell carcinoma survival: A population-based study in the Netherlands

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ABSTRACT

Background: The increased finding of kidney 'incidentalomas' and more frequent surgery in patients with renal cell cancer (RCC) metastases may have improved survival from the disease. However, recent data on survival of unselected population-based series of patients with RCC are sparse.

Methods: We collected the follow-up data for all the patients registered with RCC in the population-based cancer registry held by the Comprehensive Cancer Centre East, the Netherlands.

Results: Patients (1504) diagnosed with RCC between 1989 and 2002 were included. Eighty-three percent of all tumours were histologically confirmed; 17% of all diagnoses were based on clinical examination only. The latter group was older, had a worse stage distribution, often did not receive any kind of therapy and showed a 5-year relative survival of 8%. Five-year relative survival for patients with a histologically confirmed RCC was 60% and did not improve over the last 15 years. A low resection rate in patients with metastasis was observed, most pronounced in elderly, without a tendency of increase in more recent years.

Conclusion: The relative survival of RCC did not improve over the years. The resection rate in patients with metastasised disease did not increase over time, despite current knowledge concerning its benefit on tumour complications, time to progression and response to immunotherapy.

1. Introduction

Renal cell carcinoma (RCC) accounts for 2.5–3% of all malignancies in men and is the third most common urogenital cancer after prostate and bladder cancer.[1,2] In the Netherlands, more than 1500 patients are diagnosed with RCC, and 900 patients die from RCC each year. Similar to other countries the incidence of RCC has increased sharply in the Netherlands since the seventies but stabilized in the nineties.[3] This increase can largely be explained by the increased number of

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asymptomatic, incidental tumours, i.e. 'incidentalomas', detected as a result of the widespread use of non-invasive abdominal imaging modalities.

Patients diagnosed with RCC have a poor prognosis, which is a consequence of the frequently late clinical presentation of the disease, combined with resistance to most forms of conventional systemic therapy.[4] Since surgical resection is the only curative option for patients at this moment, early detection is of great importance. Because of the more frequent application of diagnostic imaging techniques in the past 2 decades a shift towards earlier diagnosis, smaller tumours, lower stage at diagnosis and therefore a better prognosis may be expected. However, recent data concerning the clinical characteristics and survival of unselected patients with RCC are sparse. Most of our knowledge comes from a few population-based studies [5–7] from more than a decade ago. For that reason, we performed a large population-based study in the Eastern part of the Netherlands. The aim of this study was to gain insight in the clinical characteristics, treatment modalities and survival over time of patients diagnosed with RCC between 1989 and 2002.

2. Patients and methods

All the patients diagnosed with RCC in the period 1989–2002 were identified from the population-based cancer registry held by the Comprehensive Cancer Centre East (CCCE) in the Netherlands. The CCCE is one of nine regional cancer centres with a catchment area of approximately 1.3 million inhabitants. It is served by one university hospital and seven community hospitals.

Patient inclusion criteria for this study were: diagnosed between 1st January 1989 and 31st December 2002, age at diagnosis 18 years or older and ICD-O-3 topography code C64.9.[8] In case a patient was diagnosed with two RCCs, only the first tumour was included in the analyses. In case of synchronously diagnosed tumours, the tumour with the worst stage was included. All histologically confirmed tumours were staged according to the fourth (tumours diagnosed before 1999) or the fifth (tumours diagnosed since 1999) edition of the TNM [9,10]. The most significant difference between these two TNM editions is the cut-off point between T1 and T2 tumours which changed from 2.5 to 7.0 cm tumour diameter. In order to reach uniformity, the pathology records of all T2 tumours diagnosed before 1999 were reviewed retrospectively through PALGA, a nationwide computer network and registry of histo- and cyto-pathology diagnoses (PALGA in Dutch: Pathologisch Anatomisch Landelijk Geautomatiseerd Archief). Subsequently, all T2 tumours smaller than 7.0 cm were recoded as T1 tumours. For staging of tumours which were not histologically confirmed, the Extent of Disease (Guide to Staging of Neoplasma, Extent of Disease, CCPDES) was used.

Data concerning patients' characteristics (age at diagnosis, gender), tumour characteristics (topography, histology, invasiveness, WHO grade of differentiation, lateralisation, stage, treatment) and follow-up information (vital status, date of last contact, date of death) were collected through the cancer registry. The follow-up of all the patients was completed until 1st January 2006 by the use of hospital records and by record linkage to the so-called GBA registry (Population Municipality Registration; in Dutch: Gemeentelijke Basis Administratie). This GBA registry keeps data on all deceased (and emigrated) residents in the Netherlands irrespective of the cause of death and covers the period October 1994 to March 2006. Hospital records were reviewed for patients with a last known follow-up date before October 1994. In case the follow-up of patients could not be completed until 1st January 2006, a request was submitted to the last known municipality of these patients to search the paper files concerning vital status.

Annual incidence rates were calculated per 100,000 person years for males and females, separately. Rates were age-adjusted by standardisation to the European standard population (European Standardised Rates, ESR). Because the cause of death of these patients is not available in the cancer registry, disease specific survival could not be calculated. Instead, relative survival analyses were performed according to Dickman as a good approximation of disease-specific survival[11] (www.pauldickman.com). This method adjusts crude survival rates amongst cancer patients for the expected mortality according to annual life tables of the general population matched on age, gender, calendar period and geographic area. A multivariable relative survival model is estimated using a generalised linear model with an assumed Poisson distribution for the observed number of deaths.[11] All the analyses were performed using the SAS 8.2 package (SAS Institute Inc., Cary, NC, USA 1999–2001).

3. Results

A total of 1550 patients were diagnosed with RCC between 1989 and 2002. Twenty-two patients were diagnosed with two RCCs. According to the rules mentioned before, only one tumour was included in the analyses. Tumours diagnosed by autopsy only were excluded from the analyses ($N = 46$). The age-standardized incidence rates (ESR; standardised to the Standard European population) of RCC in the CCCE region were fairly stable during the period 1989–2002 (11–12 per 100,000 amongst males and 5.5–6.5 per 100,000 amongst females; data not shown) and similar to the incidence figures in the Netherlands (www.ikcnet.nl). Similarly, no change in mortality rates was observed. In Table 1, the characteristics of all 1504 patients and tumours are presented. On average, age at diagnosis amongst males was 2.5 years lower compared to females (64.7 versus 67.1 years), probably due to the longer life expectancy of women.

3.1. *Histologically confirmed tumours*

Eighty-three percent of all tumours were histologically confirmed. The mean age at diagnosis of these patients was 64.1 years (SD = 11.2). Most patients were treated primarily with nephrectomy (85%). Approximately, 47% of all tumours were of low stage (stage I or II) whilst 50.5% were diagnosed with high stage (stage III and IV). For 2% of all the patients with a histologically confirmed diagnosis, stage was unknown. In Fig. 1, the stage distribution by gender is presented. Overall, males seem to have a higher stage more frequently compared to females. More than 60% of patients younger than 50 years of age were diagnosed with low stage disease (stages I and II) whilst this percentage was approximately 45% amongst older patients (the patients older than 50 years

Table 1 – Baseline patient and tumour characteristics of RCC patients diagnosed between 1989 and 2002

	N	Percentage (%)
Number of patients	1504	
Mean age at diagnosis (SD)	65.6 (11.6)	
Median age at diagnosis (range)	67 (24–97)	
Gender		
Males	911	60.5
Females	593	39.5
Period of diagnosis		
1989–1993	522	35
1994–1997	404	27
1998–2002	578	38
Lateralisation		
Left kidney	715	47,5
Right kidney	771	51.3
Unknown	18	1,2
Histology		
Clear cell adenocarcinoma	165	11.0
Papillary adenocarcinoma	15	1.0
Renal cell carcinoma, sarcomatoid	5	0.3
Renal cell carcinoma, chromophobe type	3	0.2
Cystadenocarcinoma	1	0.1
Granular cell carcinoma	2	<0.1
Cyst-associated renal cell carcinoma	1	<0.1
Adenocarcinoma (not further specified)	21	1.4
Renal cell carcinoma (not further specified)	1037	69.0
Only clinically confirmed	254	16.9
WHO grade of differentiation		
1	206	13.7
2	188	12.5
3	105	7.0
Unknown[a]	1005	66.8
TNM staging (histologically confirmed tumours; N = 1250)		
Stage I	370	29.6
Stage II	160	12.8
Stage III	285	22.8
Stage IV	346	27.7
Stage unknown[b]	89	7.1
Extent of disease (clinically confirmed; N = 254)		
Localized	36	14.1
Direct and/or regional extension	30	11.8
Distant metastasis	150	58.8
Unknown	38	15.3
Therapy		
Surgery	972	64.6
Surgery and lymph node dissection	53	3.5
Surgery and other therapy	28	1.9
Surgery and lymph node dissection and other therapy	1	0.1
Lymph node dissection and/or therapy on metastases	58	3.9
Other therapy (chemo-, radio-, hormonal- or immunotherapy)	22[c]	1.5
Lymph node dissection and other therapy	2	0.1
No therapy	368	24.5

a Until 2006 only the WHO differentiation grade is recorded in the NCR. Since 2006 the Fuhrman grade is also recorded in the NCR.

b The stage unknown group included T2 tumours diagnosed before 1999 but with an unknown tumour size. Re-classification following the TNM fifth edition was not possible.

c Other therapies were radiotherapy (N = 9, 41%), hormonal therapy (N = 9, 41%), immunotherapy (N = 2, 9%), chemotherapy (N = 1, 4.6%), immunotherapy and chemotherapy (N = 1, 4.6%).

of age). Furthermore, with increasing age at diagnosis the disease stage is more frequently unknown (less than 1% amongst patients younger than 50 years of age to more than 4% amongst patients older than 75) (data not shown). In Table 2, therapy by stage is presented. As expected, almost all the patients with stages I–III disease underwent nephrectomy.

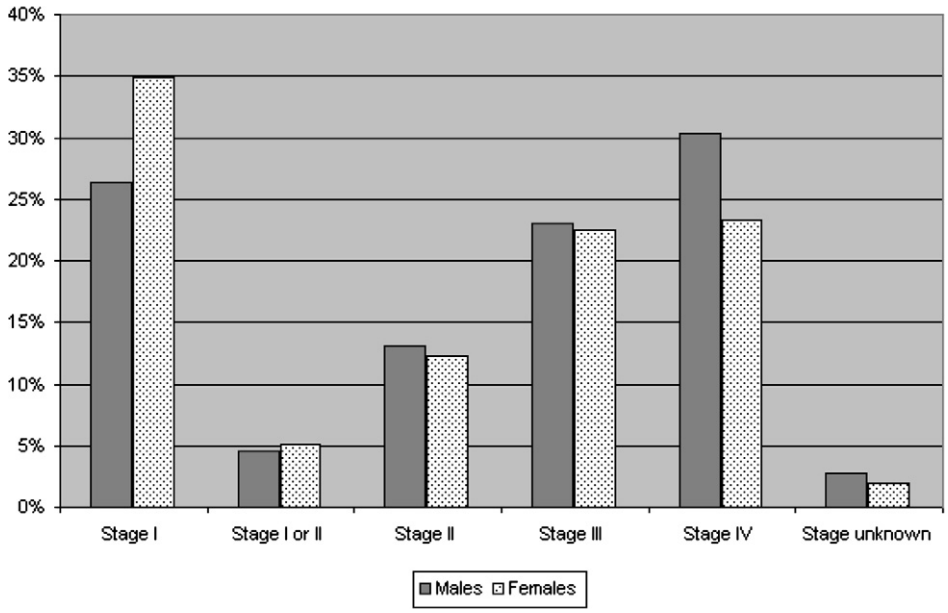

Fig. 1 – Stage distribution of histologically confirmed tumours by gender.

The patients with a stage IV tumour received surgery less frequently (<60%). Within the group of patients with stage IV tumours, the resection rate declined with advancing age (70% in the patients younger than 50 to approximately 45% in patients of 75 years and older). This trend in resection rate by age was not observed in stages I–III tumours (data not shown).

3.2. *Only clinically confirmed diagnosis*

Almost 17% of the patients had a diagnosis based on clinical information only. These patients were considerably older compared to patients with a histologically confirmed tumour (mean 73.1 versus 64.1 years). The majority of these tumours were of high stage with direct and/or regional extension or distant metastasis. By definition, none of the clinically diagnosed patients underwent nephrectomy. Most of the patients did not receive any kind of therapy at all (89%). In contrast to the histologically confirmed tumours, no clear differences were seen between males and females.

3.3. *Trends over time*

The mean age at diagnosis remained fairly stable, with an increase in age for males and a slight decrease in age for

Table 2 – Therapy according to stage

	Surgery		Surgery plus additional therapy[d]		Other therapy		No therapy		Total
	N	%	N	%	N	%	N	%	N
Histologically confirmed tumours									
Stage I	356	96.2	12	3.2	–	–	2	0.5	370
Stage II	154	96.3	5	3.1	–	–	1	0.6	160
Stage III	267	93.7	11	3.9	1	0.4	6	2.1	285
Stage IV	145	41.9	53	15.3	51	14.7	97	28.0	346
Stage unknown[a]	50	56.2	1	1.1	1	1.1	37	41.6	89
Total	972	77.8	82	6.6	53	4.2	143	11.4	1250
Clinically confirmed tumours									
Localized					–	–	36[b]	100.0	36
Direct and/or regional extension					1	3.3	29	96.7	30
Distant metastasis					27	18.0	123	82.0	150
Unknown					1	2.6	37	97.4	38
Total					29[c]	11.4	225	88.6	254

a The stage unknown group included T2 tumours diagnosed before 1999 but with an unknown tumour size. Re-classification following the TNM fifth edition was not possible.

b Most of these patients had also other malignancies like lung cancer, colorectal cancer, etc. Probably the reason for not treating them.

c These 29 patients received different treatments: 4 patients were treated with hormonal therapy, 4 with radiotherapy on primary tumour, and 21 with radiotherapy on metastases.

d Additional therapy can be lymph node dissection, therapy on metastases, hormonal therapy or radiotherapy.

females over time. The median tumour diameter decreased during the period 1989–2002, which was most pronounced for females. The median tumour diameter amongst males was 70 mm in 1989 and 65 mm in 2002 whilst for females these numbers were 80 and 57, respectively. However, this decrease was not reflected in the stage distribution over time. Only the number of tumours with stage unknown decreased over time towards zero, reflecting a better quality of staging. Over time the resection rate increased; in the earlier years histologically confirmed tumours were treated surgically in 80% of all the cases; in more recent years this percentage increased to almost 90%. For patients with stage IV tumours, the percentage of patients treated surgically remained stable over the period (approximately 55–60%). However, the number of patients not receiving any kind of treatment decreased slightly. A similar trend was seen amongst patients with a clinical diagnosis; in the period 1989–1993, 95% of the patients did not receive any treatment whilst in the period 1998–2002 this percentage was approximately 85%.

3.4. *Survival*

The 1-, 3-, 5- and 10-year crude survival of all the patients was 68%, 51%, 44% and 32%, respectively. The relative survival was 71%, 56%, 52% and 44%, respectively. Fig. 2 shows the relative survival rates (RSR) according to stage. In Table 3a–3c, the survival rates are presented. Overall, the 5- and 10-year RSRs amongst females were approximately 4.5% better than amongst males. Stage-specific RSRs for stage I and II were better in females compared to males (stage I: males 87.9% versus females 92.2%; stage II males 67.2% versus females 78.9%). As expected, patients with a clinically confirmed tumour had a worse survival than the patients with a histologically confirmed tumour (5-year survival is 7% versus 60%). No clear improvement was seen in the survival of patients diagnosed in the period 1998–2002 compared to the two earlier periods. However, when only histologically confirmed tumours were included, patients diagnosed in the period 1998–2002 seem to have a slightly better 5-year RSR (64% compared to 59% and 57%, respectively). The patients with an advanced age at diagnosis had a dismal prognosis as compared to younger patients, even when adjusted for expected mortality (5-year RSRs are 67% and 36%, for patients younger than 50 and older than 75 years, respectively). Patients treated surgically had a 5- and 10-year RSR of 72% and 63%, whereas patients treated with other modalities than surgery had a much worse survival. The patients diagnosed with stage IV disease who had been treated surgically showed a much better survival as compared to the patients receiving other or no treatment (5-year RSR is 26% versus 2.5% and 0%, respectively). The patients younger than 70 years with a low stage tumour (stages I and II, localised disease) treated surgically showed a better survival after 5 and 10 years (i.e. 86% and 78%) than patients older than 70 years with similar tumours and similar treatment (78% and 71%). However, in patients with higher stage disease (stages III and IV) this survival difference between younger (5-year RSR: 52% and 10-year RSR: 39%) and older patients (5-year RSR: 48% and 10-year RSR: 44%) disappeared.

In Tables 4a and 4b, the results of the multivariable Poisson regression analyses are presented. Concerning the histologically confirmed tumours, stage appeared to be the most important prognostic factor for survival, next to the grade of differentiation and therapy. Age at diagnosis, gender and period of diagnosis have no additional prognostic value after adjustment for stage, therapy and grade. For the clinically diagnosed patients only stage and to a lesser extent age at diagnosis were of independent prognostic value. A multivariable analysis including only patients with stage IV tumours

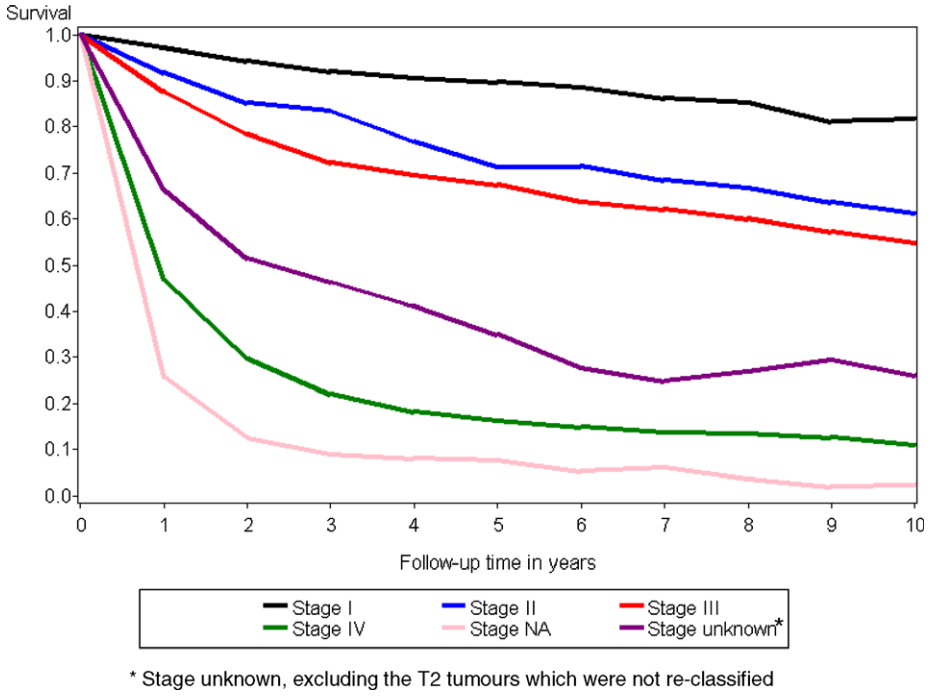

Fig. 2 – Relative survival by stage (NA are the tumours with a clinical diagnosis only).

Table 3a – Relative survival in all the patients with renal cell carcinoma

Item	N	1-year survival (95% CI)[a]	5-year survival (95% CI)	10-year survival (95% CI)
All	1504	70.6 (68.1–79.6)	51.7 (48.7–54.7)	44.2 (40.5–48.0)
Gender				
Males	911	70.2 (67.0–73.3)	49.9 (46.0–53.7)	42.4 (37.6–47.4)
Females	593	71.1 (67.1–74.8)	54.5 (49.7–59.1)	46.8 (40.9–52.8)
Histology				
Histologically confirmed	1250	79.4 (76.9–81.7)	60.2 (56.9–63.4)	51.9 (47.7–56.2)
Only clinically confirmed	254	25.7 (20.3–31.5)	7.6 (4.1–12.7)	–
WHO grade of differentiation				
1	206	93.6 (88.7–96.9)	80.6 (72.6–87.4)	69.2 (57.1–80.5)
2	188	86.4 (80.1–91.1)	58.7 (50.0–66.9)	44.6 (34.3–55.1)
3/4	105	59.3 (49.0–68.4)	39.9 (29.4–50.5)	32.4 (20.6–45.6)
Unknown[b]	1005	64.0 (60.8–67.1)	45.6 (42.0–49.2)	40.1 (35.8–44.7)
TNM staging[c]				
Stage I	370	97.3 (94.5–99.1)	89.9 (84.7–94.2)	81.8 (73.3–89.4)
Stage II	160	91.9 (85.8–95.8)	71.4 (62.1–79.6)	61.2 (49.2–72.6)
Stage III	285	87.7 (82.9–91.5)	67.4 (60.2–74.1)	54.8 (45.1–64.4)
Stage IV	346	46.9 (41.4–52.2)	16.3 (12.3–20.9)	11.1 (7.2–16.0)
Stage not applicable[d]	254	25.7 (20.3–31.5)	7.6 (4.1–12.7)	2.5 (0.3–11.7)
Stage unknown[e]	30	66.3 (45.7–81.3)	35.0 (16.5–56.4)	26.2 (8.3–54.6)
Period of diagnosis				
1989–1993	522	69.7 (65.3–73.7)	51.6 (46.4–56.7)	47.3 (41.4–53.4)
1994–1997	404	72.2 (67.3–76.6)	50.2 (44.5–55.8)	39.5 (33.4–45.8)
1998–2002	578	70.3 (66.2–74.0)	53.0 (48.1–57.7)	–
Age group				
Younger than 50 years	145	85.5 (78.6–90.4)	66.9 (58.3–74.2)	59.7 (49.5–68.7)
50–74 years	1010	72.7 (69.8–75.5)	54.2 (50.7–57.7)	45.1 (40.8–49.5)
75 years and older	349	57.2 (51.3–62.8)	35.9 (28.9–43.4)	37.0 (25.7–50.4)
Therapy				
Surgery	972	88.6 (86.2–90.7)	71.7 (68.0–75.1)	62.8 (57.8–67.8)
Surgery plus other therapy	82	64.8 (53.2–74.4)	35.6 (24.6–47.1)	13.4 (3.0–32.6)
Other therapy	82	32.6 (22.6–43.0)	4.2 (1.0–11.2)	–
No therapy	368	30.7 (25.9–35.8)	9.4 (6.1–13.8)	6.3 (3.0–11.6)

a 95% CI: 95% confidence interval.
b Until 2006 only the WHO differentiation grade is recorded in the NCR. Since 2006 the Fuhrman grade is also recorded in the NCR.
c Patients with stage I/II excluded.
d Stage not applicable: only clinically confirmed tumours.
e Stage unknown, excluding the T2 tumours which were not re-classified.

showed a clear beneficial effect of surgery on survival (after adjustment for grade, age, gender and period of diagnosis). The RSR of other therapy and no therapy compared to surgery is 2.3 (95% CI: 1.6–3.3) and 5.6 (95% CI: 4.1–7.6), respectively (data not shown).

4. Discussion

In this population-based study, we evaluated the clinical characteristics and survival of patients diagnosed with RCC. Seventeen percent of these patients were diagnosed with a RCC without histological confirmation; these patients appeared to be 9 years older at the time of diagnosis, often received no treatment, and had a very poor prognosis. Elderly patients presented themselves more frequently with higher stage disease. Furthermore, older patients with stage IV tumours were less likely to be treated surgically in comparison with younger patients. A putative explanation for these observations is that in the older patients a poor performance status and/or the presence of severe co-morbid conditions may have discouraged clinicians to perform surgery resulting in a poor prognosis. Another reason could be that, just because of higher age or low performance status, medical examinations may have been less thorough resulting in a clinical diagnosis only and/or less extensive therapy. In this study, data concerning co-morbid conditions and performance status were not available and therefore its influence on treatment decision (whether justified or not) and survival could not be studied. But it is very likely that confounding by indication prohibits a valid evaluation of treatment effects.

The median tumour size in females slightly decreased over time whereas the tumour size in males remained more or less stable. Females also presented more frequently with low stage disease. A possible explanation for this observation may be that RCC is detected earlier in females than in males because females undergo diagnostic procedures more frequently, with a higher chance of an incidental finding of a renal mass. In order to verify this statement we examined the

Table 3b – Relative survival in patients with histologically confirmed renal cell carcinoma

Item	N	1-year survival	5-year survival	10-year survival
All	1250	79.4 (76.9–81.7)	60.2 (56.9–63.4)	51.9 (47.7v56.2)
Gender				
Males	775	78.1 (74.8–81.1)	57.0 (52.7–61.1)	49.2 (43.8–54.7)
Females	475	81.5 (77.5–84.9)	65.3 (60.1–70.3)	56.1 (49.3–62.9)
WHO grade of differentiation				
1	206	93.6 (88.7–96.9)	80.6 (72.6–87.4)	69.2 (57.1–80.5)
2	188	86.4 (80.1–91.1)	58.7 (50.0–66.9)	44.6 (34.3–55.1)
3/4	105	59.3 (49.0–68.4)	39.9 (29.4–50.5)	32.4 (20.6–45.6)
Unknown	751	76.5 (73.2–79.6)	57.7 (53.5–61.9)	51.7 (46.3–57.1)
TNM staging				
Stage I	370	97.3 (94.5–99.1)	89.9 (84.7–94.2)	81.8 (73.3–89.4)
Stage II	160	91.9 (85.8–95.8)	71.4 (62.1–79.6)	61.2 (49.2–72.6)
Stage III	285	87.7 (82.9–91.5)	67.4 (60.2–74.1)	54.8 (45.1–64.4)
Stage IV	346	46.9 (41.4–52.2)	16.3 (12.3–20.9)	11.1 (7.2–16.0)
Stage unknown	30	66.3 (45.7–81.3)	35.0 (16.5–56.4)	26.2 (8.3–54.6)
Period of diagnosis				
1989–1993	444	76.8 (72.3–80.7)	58.8 (53.1–64.2)	54.1 (47.4–60.7)
1994–1997	342	79.0 (74.0–83.2)	56.7 (50.5–62.6)	45.3 (38.4–52.2)
1998–2002	464	82.1 (78.1–85.6)	64.3 (58.8–69.4)	–
Age group				
Younger than 50 years	140	86.5 (79.5–91.2)	68.6 (59.9–75.9)	61.2 (50.8–70.2)
50–74 years	889	79.5 (76.5–82.1)	61.1 (57.3–64.7)	51.1 (46.3–55.9)
75 years and older	221	74.2 (67.0–80.4)	49.0 (39.3–59.1)	53.4 (37.1–72.2)
Therapy				
Surgery	972	88.6 (86.2–90.7)	71.7 (68.0–75.1)	62.8 (57.8–67.8)
Surgery plus other therapy	82	64.8 (53.2–74.4)	35.6 (24.6–47.1)	13.4 (3.0–32.6)
Other therapy	53	38.8 (25.6–51.9)	6.5 (1.6–16.7)	–
No therapy	143	37.8 (29.5–46.2)	10.8 (5.5–18.2)	9.2 (3.9–17.8)

Table 3c – Relative survival in patients with clinically confirmed renal cell carcinoma

Item	N	1-year survival	5-year survival
All	254	25.7 (20.3–31.5)	7.6 (4.1–12.7)
Gender			
Males	136	23.2 (16.2–31.0)	6.6 (2.5–14.0)
Females	118	28.6 (20.5–37.2)	8.7 (3.8–16.7)
Extent of disease			
Localized	36	51.3 (33.1–67.7)	20.8 (7.0–42.2)
Direct and/or regional extension	30	21.2 (8.6–37.7)	5.0 (0.4–21.9)
Distant metastasis	150	16.9 (11.3–23.6)	–
Unknown	38	41.5 (24.8–58.0)	31.9 (13.6–56.1)
Period of diagnosis			
1989–1993	78	27.9 (18.1–38.7)	7.4 (2.0–18.4)
1994–1997	62	33.0 (21.2–45.5)	12.4 (4.0–27.6)
1998–2002	114	20.4 (13.4–28.5)	5.4 (1.9–11.7)
Age group			
<50 years	5	60.1 (12.6–88.4)	20.3 (0.8–59.0)
50–74 years	121	22.7 (15.6–30.6)	3.1 (0.8–8.0)
75 years and older	128	27.4 (19.5–36.0)	12.7 (5.9–23.1)
Therapy			
Other therapy	29	21.3 (8.6–37.8)	–
No therapy	225	26.3 (20.5–32.5)	8.7 (4.7–14.5)

number of abdominal ultrasounds requested by general practitioners in 2005 and 2006 in a large teaching hospital in the region of the CCCE, which is more or less representative for most community hospitals in the Netherlands. Indeed, it appeared that from all requested ultrasounds approximately two-thirds were performed in females, not including the regular ultrasounds in pregnant women (2005 and 2006: 13,016 ultrasounds, 4287 in males and 8729 in females).

As expected, surgery was the principal treatment for patients with a localised RCC. Unfortunately, no distinction could be made in radical nephrectomy and partial nephrectomy or open nephrectomy versus laparoscopic nephrectomy. Therefore no differences in long term oncologic outcome could be studied. No clear differences between the different surgical interventions are expected, however, based on the current literature.[12–17]

Concerning metastatic RCC, only 55–60% of the patients in this study were treated with nephrectomy. Although nephrectomy in patients with metastatic spread of a RCC will probably not be curative, it may be beneficial because of prevention of tumour complications like bleeding and flank pain, delay of progression due to removal of the source of new metastases and improvement of response to immunotherapy possibly leading to a better survival and quality of life.[18,19] In 2001, the results of two randomized controlled trials, one EORTC (European Organisation for Research and Treatment of

Table 4a – Multivariable Poisson regression analysis (histologically confirmed tumours)

Item	Reference	Index	Relative excess risk	95% confidence interval
Stage	Stage I	Stage II	3.5	1.8–6.8
		Stage III	4.8	2.6–9.0
		Stage IV	18.4	10.1–33.6
		Stage Unknown	4.8	2.1–10.6
Therapy	Surgery	Surgery plus other therapy	1.0	0.7–1.5
		Other therapy	2.4	1.7–3.5
		No therapy	5.6	4.2–7.6
WHO grade of differentiation	Grade I	Grade II	2.3	1.5–3.6
		Grade III /IV	3.1	1.9–4.9
		Grade Unknown	1.6	1.1–2.4
Period	1989–1993	1994–1997	1.4	1.1–1.8
		1998–2002	1.1	0.9–1.5
Age	Younger than 50 years	50–74 years	1.1	0.8–1.6
		75 years or older	1.1	0.7–1.7
Gender	Males	Females	1.0	0.8–1.2

Table 4b – Multivariable Poisson regression analysis (only clinically confirmed tumours)

Item	Reference	Index	Relative excess risk	95% confidence interval
Stage	Localized	Local/regional extension	3.1	1.7–5.5
		Metastasis	4.4	2.8–7.0
		Unknown	1.3	0.7–2.4
Therapy	Other therapy	No therapy	1.1	0.7–1.7
Age	Younger than 50 years	50 – 74 years	2.7	0.9–7.6
		75 years and older	2.5	0.9–7.2
Period	1989–1993	1994–1997	1.0	0.7–1.4
		1998–2002	1.3	0.9–1.8
Gender	Males	Females	0.8	0.6–1.1

Cancer) trial[20] and the other SWOG (Southwest Oncology Group) trial[21], were published showing that cytoreductive surgery in combination with immunotherapy delayed time to progression and improved survival compared to immunotherapy alone. Therefore, cytoreductive surgery is the recommended therapy for metastatic RCC patients who are estimated to be fit enough to undergo immunotherapy following surgery. However, this study shows that this knowledge has not (yet) changed the treatment policy in the general health care environment since the resection rate in metastatic patients did not increase over time. Possibly, future studies including more recently diagnosed patients might show an increase in resection rate.

Our data show that the stage distribution has not changed over the years (despite the trend amongst females towards slightly smaller tumours). As stage is the most important prognostic factor, it is not surprising that the survival of patients with RCC has not improved over the last 15 years. The 5-year relative survival found in this study varied between 90% for patients with stage I tumours and 16% for patients with a stage IV tumour. The SEER cancer registry in the US reported 5-year survival rates for localized, regional and distant disease of 90%, 61% and 9% in the period between 1988 and 2003 (www.seer.cancer.gov). It should, however, be noted that these tumours were staged differently and also include tumours of the renal pelvis. Remarkably, a small part of the patients with a clinical diagnosis only or with a stage IV tumor, who usually have a poor prognosis, were still alive after 5 years. Amongst the 254 patients with a clinical diagnosis, 11 (4%) were still alive. For the 348 patients with a stage IV tumour 38 (11%) were still alive after 5 years. Although we made a huge effort to reach a 100% complete follow-up, we cannot exclude the possibility that we have missed the death of a single patient. The prolonged survival in this small group of patients may be caused by the sometimes indolent natural behaviour of this tumor, which is known even when the tumour is already metastasised at time of diagnoses.

Until very recently, metastatic RCC has been treated with cytokine-based therapy (with prior radical nephrectomy when patients have a good performance). Recent insights have demonstrated that the majority of clear cell renal cell cancers harbour abnormalities in the von Hippel Lindau (VHL) gene, which plays a key role in the stimulation of angiogenesis by vascular endothelial growth factor (VEGF) in this highly vascularised tumour.[4] This has opened interesting new treatment strategies including blockade of VEGF with the

monoclonal antibody bevacizumab (Avastin®) and inhibition of VEGF receptor tyrosine kinases (with orally applied small molecules such as sunitinib (Sutent®) and sorafenib (Nevexar®). For sorafenib a prolongation of progression-free survival in cytokine refractory patients has been demonstrated.[22] For sunitinib improved response rates and prolongation of progression-free survival compared to alfa-interferon treatment in untreated patients has been demonstrated.[23] These observations have led to the approval of these drugs by health care authorities which will subsequently lead to an increased application of these drugs in general hospitals. It will be interesting to see whether this will lead to an improvement in prognosis in the near future in unselected patients.

Conflict of interest statement

None declared.

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