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Metastatic renal cell carcinoma: Results of a population-based study with 25 years follow-up

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ABSTRACT

Background: Renal cell carcinoma (RCC) is the sixth leading cause of death in developed countries. A third of all RCC patients are confronted with metastatic disease. Since their approval in 2005 and 2006 in the USA, new targeted therapies may lead to substantial progress. Thus, the aim of this cohort study was to present clinical characteristics and survival in metastatic RCC in a population-based sample before widespread implementation of these new therapies.

Methods: Patients (2264) with metastatic RCC registered between 1978 and 2005 in the cancer registry of Munich, Bavaria were analysed.

Results: Median survival and 5 year relative survival from the 1st metastases were 14.4 months and 21%, respectively. Median survival has slightly improved from 13.2 months in 1978–1987 to 15.6 months since 2002.

Conclusion: Survival of patients with metastatic RCC did not substantially improve within the last three decades. Assuming that new targeted therapies are successful in the treatment of metastatic RCC, population-based data like these can provide a basis for assessing the progress shown in clinical studies and for surveying critically the future implementation of new therapies in routine care.

1. Introduction

Renal cell carcinoma (RCC) is the sixth leading cause of cancer death in developed countries with an incidence/mortality rate of 10.4/4.6 per 100,000 for men and 5.0/2.1 per 100,000 for women (world standard).[1] In Germany, RCC accounts for 4.7% of all malignancies in men,[2] and in the United States for 2–3%.[3] The main cause of tumour-related death is metastatic disease. In the United States, about 25% of patients with kidney cancer present with distant metastases at initial diagnosis and a further proportion of 8% develop metastases during the course of the disease.[4] Therefore, a third of all patients are confronted with a poor prognosis and a median survival time of less than 1 year from the first metastasisation.

Until today RCC remains resistant against any chemotherapy, and immunotherapy has not led to great improvement of survival in metastatic disease.[5,6] The new targeted therapies as tyrosine kinase inhibitors and neutralising antibodies against the vascular endothelial growth factor (VEGF) have raised great hopes for the near future with at least prolonged disease-free survival.[7–10]

It is the purpose of this report to provide a basis for knowledge of prognostic factors, and survival and progression patterns in metastatic RCC in a population-based sample for

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evaluating any clinical studies, designing further studies and evaluating the implementation of new therapies in routine care. Towards this aim, the Munich Cancer Registry (MCR) documented and analysed data of a large cohort of RCC patients over 27 years.

2. Patients and methods

2.1. Data collection

The MCR was established in 1978 as the clinical registry of the Munich Cancer Centre. Initially, the MCR cooperated with the two University hospitals in Munich and since 1988 collaborations have extended to all hospitals in the city and district of Munich, a region with 2.3 million people. The Bavarian Cancer Registration Law was enforced in 2000 and resulted in an enlargement of the enrolment area to 3.8 million people in 2002 and to 4.4 million people in 2007.

Since 1978, data about primary disease characteristics such as TNM stage, histology, WHO grade and therapy were collected from MCR-affiliated hospitals using tumour-specific forms. Additionally, all pathological reports are available since 1994, and were used to supplement information obtained from the hospitals.

Life-status was maintained systematically through death certificates and the inhabitants' registration offices for patients with a cancer diagnosis since 1978. Thus, follow-up was available in more than 90% of all cases.

Additionally, the hospitals provided details concerning any kind of disease progression. Completeness concerning local and distant recurrences clearly differs. Surgically treated and histopathologically confirmed recurrences are almost completely documented from pathological reports. The documentation of distant metastases without histopathological confirmation is estimated to contain at 70%. However, the rate of death certificate only (DCO) cases is 10%.

Information about therapy for distant metastases was only available when it was part of a primary therapy, but detail was lacking. Chemotherapy regimes were not routinely documented in the cancer registry. Thus, medical progress can only be assessed by comparing periods of time.

The advantage of the MCR data is their representativeness with respect to patients in routine care. The patient population reflects the age distribution with inherent differences in performance status and comorbidity and with the corresponding data of the primary RCC tumour.

2.2. Patient and tumour characteristics

To assess medical progress, the cohort was divided into three periods of time 1978–1987, 1988–1997 and 1998–2005. These periods represent the development of the MCR from a Clinical Registry of University Hospitals to a population-based registry. The first cohort mostly represents patients of university hospitals. These patients would have been treated by the gold standard therapy of that time period. The second cohort represents the change to a population-based registry and

Table 1 – Demographic and clinical characteristics documented by the MCR 1978–2005

	1978–1987	1988–1997	1998–2005
Number of patients	1281	3929	3323
Mean age at diagnosis ± SD (years)	58.5 ± 11.4	62.2 ± 11.6	64.1 ± 11.6
Male (%)	63.0	61.9	63.5
pT1 (%)[b]	11.8	9.1	61.6
pT2 (%)	48.0	56.0	11.5
pT3/4 (%)	40.3	35.0	26.9
pN+ (%)	12.1	7.8	6.4
Grading G3 (%)	20.7	16.0	16.6
Primary M1 (%)	17.3	11.3	13.0
Nephrectomy (%)	65.7	80.6	77.2
No surgical therapy (%)	4.4	1.6	0.9
Radiation therapy (%)	24.3	3.2	3.1
Chemotherapy (%)	3.8	3.2	2.6
Immunotherapy (%)	0.3	3.3	3.4
Median survivor follow-up (years)	20.9 ± 2.7	11.6 ± 2.7	3.8 ± 2.1
Lost to follow-up (%)[a]	19.8	14.4	10.0
Median observation time of patients lost to follow-up (years)	3.7 ± 4.5	2.4 ± 3.5	0.7 ± 1.4
Number of locoregional recurrences (%)	8.2	3.4	1.9
Number of deaths (%)	63.4	46.5	24.8
5 years/10 years relative survival (%)	71.1/62.1	77.5/67.2	76.7
Number of MET primary M1 and M0[d] (%)	43.1	25.5	22.2
Number of multiple MET initially (% of[d])	26.1	27.5	36.5
Median MET-free interval (years) [c]	3.6	3.3	1.3
Median survival 1st MET to death by period of MET diagnosis (months)	13.2	14.4	15.6

a *Lost to follow-up*: Last life-status at least 1 year before MET metastases.
b *Consider a shift in pT*: Up to 1997 tumours less or equal to 2.5 cm are categorised as pT1, since September 1997 tumours less or equal to 7 cm are categorised as pT1.
c For primary M0 only.
d All patients with metastatic disease (at primary diagnosis (M1) or in follow-up (M0)).

Table 2 – Distribution of metastatic sites in metastases at primary diagnosis (M1), first metastases in follow-up (M0), in M0 by single and multiple sites and in all further metastases

Site of metastatic disease (%)	Primary M1	Primary M0 (MET in follow-up)	Primary M0 (MET in follow-up)		
	Number of patients $n = 1084$ Number of sites $n = 1550$[b]	1st MET Number of patients $n = 1180$ Number of sites $n = 1468$[d]	1st MET single site Number of patients $n = 958$ Number of sites $n = 958$[e]	1st MET multiple sites Number of patients $n = 222$ Number of sites $n = 510$[e]	Not 1st MET Number of patients $n = 396$ Number of sites $n = 592$
Lung	53	40	33	69	24
Bone	36	25	23	35	27
Liver	15	11	6	31	11
Lymph nodes	11	10	6	28	11
Brain	7	10	8	18	19
Adrenal gland	8	3	3	5	4
Urogenital	2	2	2	7	4
Retroperitoneal/ Peritoneal	2	3	1	9	4
Thyroid	1	5	5	5	4
Others[a]	9	17	14	25	42
Sum[c]	144	126	100	232	150

MET metastasis.

a Skin, soft tissue, other abdominal and unclearly documented MET.

b In every patient only the first MET of each site is counted.

c Sum of metastatic sites, Number of patients is 100%.

d Sum of both.

e In 3rd and 4th column.

increasingly includes those patients who are too old, too comorbid or unwilling to seek treatment in the university hospitals; therefore the proportion of patients with up-to-date treatment may have decreased. The third cohort represents the population-based sample of the enrolment area. The cut-point 1997/1998 takes into consideration the modification of the T-Classification of the UICC between T1 and T2 (up to 1997: T1 $\leqslant$ 2.5 cm, T2 > 2.5 cm; since 1998: T1 $\leqslant$ 7 cm, T2 > 7 cm).

From 1978 to 2005, a total of 9357 kidney cancers were registered and observed until 1st December, 2005. In this analysis, patients with previous or synchronous secondary malignancies and DCO cases were not included. We focused on survival after the first metastasis and the patterns of metastatic sites. We discriminate between patients with distant metastases at primary diagnosis (M1) and those with distant metastases detected after primary treatment (M0). In addition, we distinguish between single and multiple metastases at the first diagnosis of metastases. In the analyses, each metastatic site is counted only once in a patient, regardless of multiple metastases in the same site. The disease-free survival before the first distant metastasis is not presented, because we must presume an 'under-estimated' proportion of patients with metastasis in the follow-up due to the 10% rate of DCO cases. This fact may interfere with survival after the first metastasis. In the worst case, these patients represent a sample of patients with the most aggressive form of RCC or in the worst general condition, who were never admitted to a surgical department in the enrolment area. Therefore, the survival after the first metastasis may be overestimated.

2.3. *Statistical analysis*

The MCR organises data in an ORACLE database. All statistical analyses were run in SAS (Statistical Analysis System, Release 8.2). Overall survival after metastasis was estimated by the Kaplan–Meier method. The Kaplan–Meier curves discontinue when less than 10 patients at risk remain. Relative survival was computed by the ratio of the observed survival rate to the expected survival rate, and should be an adequate approximation for tumour-specific survival. The expected survival time of age and gender matched individuals was calculated from the life tables of the general German population. Essentially, survival after the first distant metastasis is tumour-specific; therefore we present the overall survival.

The Cox proportional hazard model was used to assess the prognostic influence of patient and tumour characteristics on survival after the first metastasis. We present hazard ratios (HR) and 95% confidence intervals (CI).

3. Results

3.1. *Patient and disease characteristics through time periods*

8533 Patients without previous or synchronous other malignancies were included in the analysis. Table 1 shows the patients' characteristics in three time periods. Compared to the first period, patients nowadays are 5 years older at the first diagnosis. The proportion of male patients remained un-

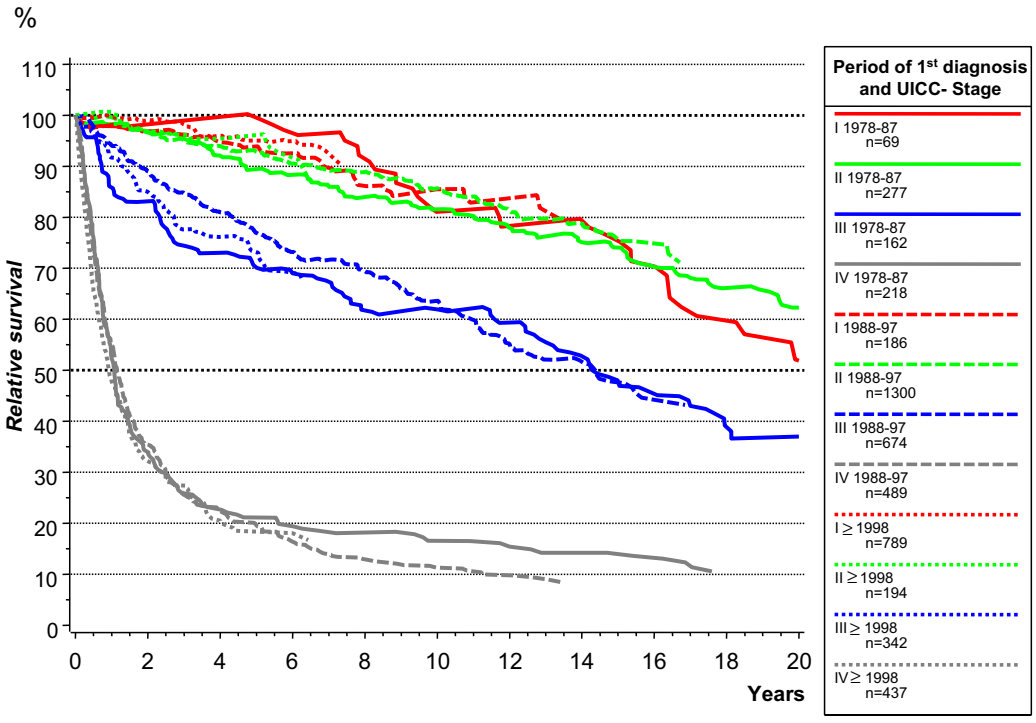


Fig. 1 – Relative survival of all kidney cancer patients by period of diagnosis and UICC-stage.

changed at approximately two-thirds. The proportion of pT3/4-tumours decreased from 40% to 27% in the first and the last time periods, respectively. Because of the modification of the T-classification at the end of 1997, the proportion of pT1 has increased to 62%. Surgical therapy of the primary tumour is standard. Less than 5% of patients have undergone either systemic immuno-, or chemo- or radiation therapy.

The proportion of primary distant metastatic disease (M1) decreased from 17% to 13.0%. Median survival in metastatic disease hardly increased over almost three decades.

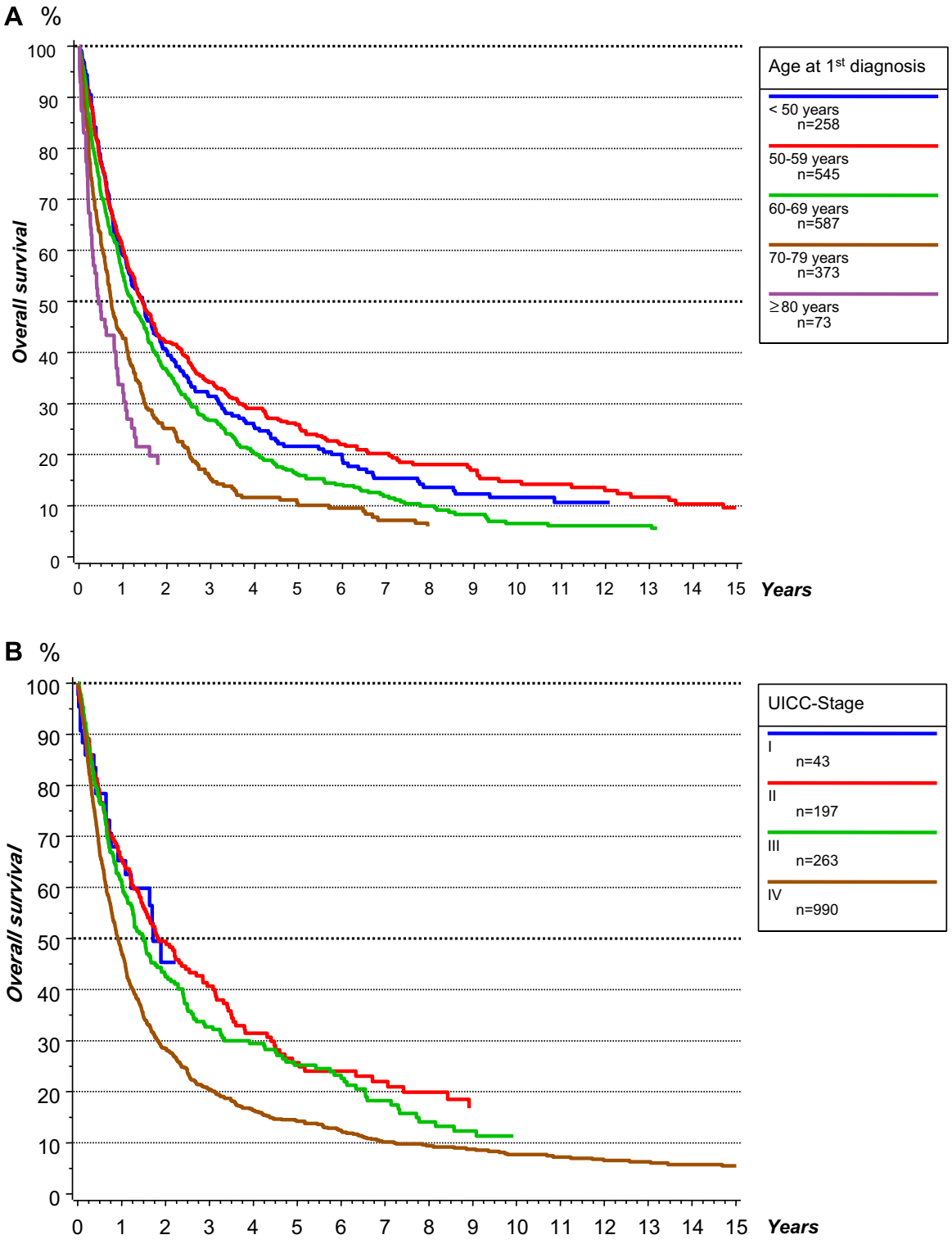
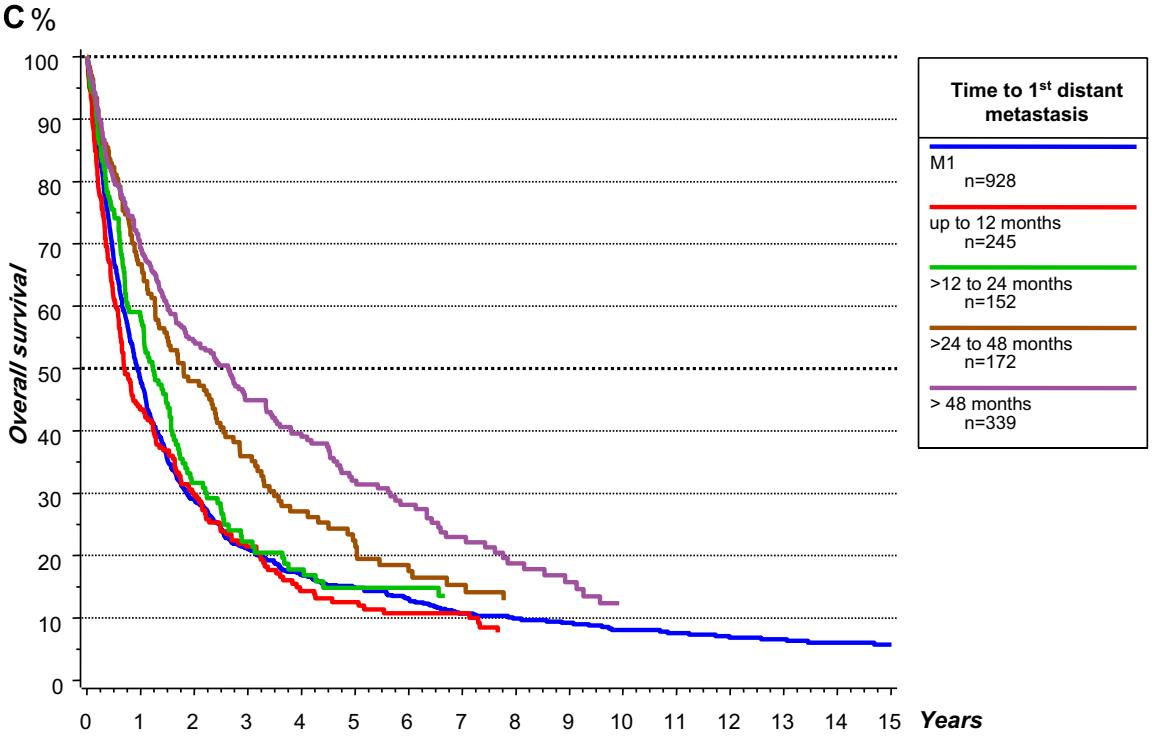


Fig. 2 – Overall survival beginning with the first metastasis stratified A by age, B by UICC-Stage, C by metastasis-free interval, D by period of diagnosis of 1st metastasis.



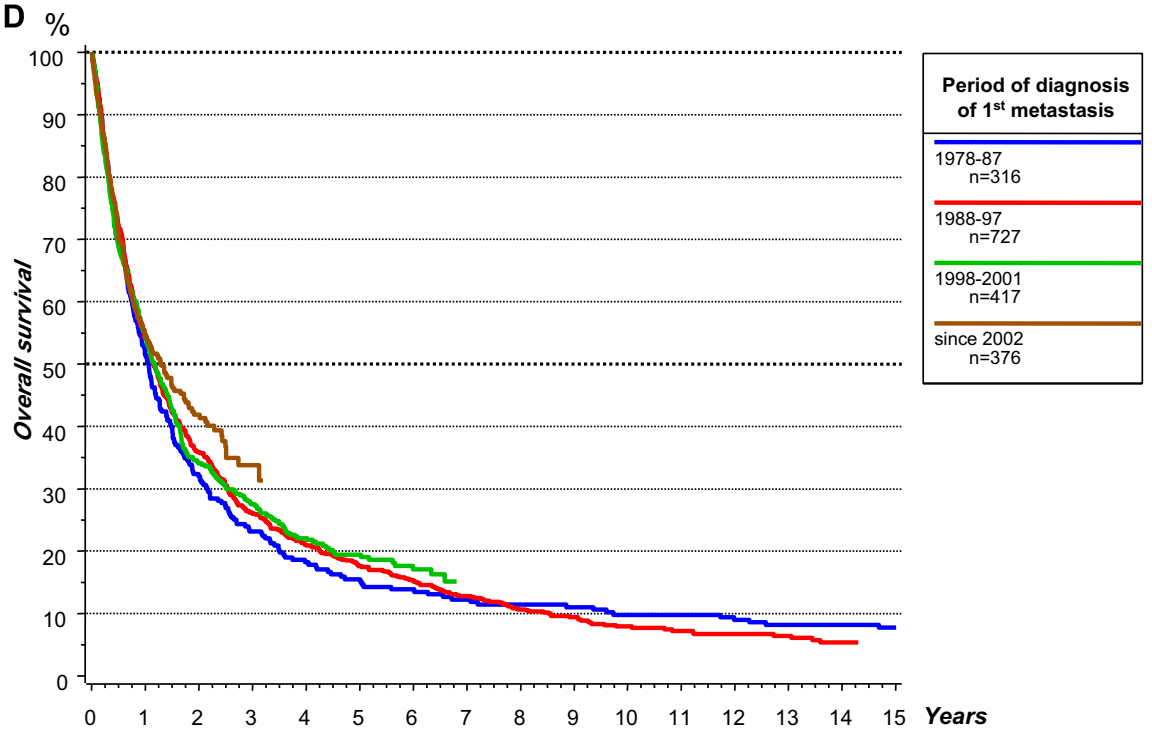


Fig. 2 (*continued*)

3.2. *Metastases*

At the initial diagnosis, 1084 patients (13%) had an M1-stage (M1-patients) with 1550 metastatic sites. After treatment for local RCC, 1180 patients (14%) relapsed in the follow-up with 1468 distant metastases. M1-patients had on average 1.4 sites of metastases, those with distant relapse in the follow-up had on average 1.2 sites. Table 2 shows the distribution of metastatic sites. Over half (53%) of primary M1-patients had metastases of the lung, 36% had metastases of the bone and 15% of the liver. Fewer patients with first metastases at follow-up (data collected until December 2005) developed

metastases of the lung, bone and liver (40%, 25% and 11%, respectively); however the distribution of metastatic sites was similar to M1-patients.

3.3. Survival

The 5 year relative survival of all patients with kidney cancer has only slightly improved over the last 30 years, from 71% in the period 1978–1987 to 77% in 1998–2005. It is presented stratified by UICC stage in Fig. 1.

Survival from the first metastases, stratified by important prognostic factors, is presented in Fig. 2 and Table 3. Survival from any metastasis stratified by metastatic site is shown in Fig. 3.

It is important to consider that the patient counts in the survival curves and the multivariate analysis vary due to missing values. The 5 year overall survival of all patients with metastases (beginning at 1st MET) was 19% (relative survival 21%).

The multivariate Cox proportional hazard model in Table 4 shows that the strong prognostic factors for survival in M1-patients at primary diagnosis are tumour and lymph node stage and histological grade, whereas age and time period of primary diagnosis have no significant influence. For M0-patients, age and lymph node stage demonstrate a significant influence on survival, although the MET-free interval does not. A significant influence on M0-patient survival was observed for the period of diagnosis, yet the association is heterogeneous and shows no trend.

4. Discussion

The MCR has recorded population-based RCC incidence since 1998, which provides an important epidemiologic reference

Table 3 – Survival from 1st metastasis by patient characteristics

Overall and relative survival (%)	*n*	1 year (95% CI)[a]	5 year (95% CI)[a]	5 year relative survival	Median survival in months
All	1836	57 (53–58)	19 (17–21)	21	13.2
Age at 1st diagnosis (years)					
<50	258	59 (53–65)	22 16–27)	22	16.8
50–59	545	60 (56–65)	25 (22–30)	26	16.8
60–69	587	55 (51–59)	16 (13–20)	18	14.4
70–79	373	43 (38–48)	10 (6–14)	13	8.4
⩾80	73	32 (21–43)	5 (0–11)	7	4.8
UICC-stage					
I	43	66 (50–81)	28 (7–49)	n.c.	22.8
II	197	65 (58–72)	25 (18–32)	26	21.6
III	263	61 (55–67)	25 (19–31)	26	18.0
IV	990	47 (44–50)	14 (12–17)	16	10.8
Time to 1st MET (months)					
M1	928	48 45–51)	15 (12–17)	17	10.8
⩽12	245	44 (37–50)	13 (8–17)	13	8.4
>12 to ⩽24	152	58 (50–67)	15 (8–21)	15	14.4
>24 to ⩽48	172	67 (59–74)	22 (15–30)	23	21.6
>48	339	70 (64–74)	32 (26–38)	34	31.2
Period of diagnosis of 1st MET					
1978–1987	316	52 (47–57)	16 (12–20)	17	13.2
1988–1997	727	54 (52–59)	18 (16–21)	19	13.2
1998–2001	417	54 (52–61)	19 (16–23)	22	14.4
Since 2002	376	55 (52–60)	19 (14–24)	20	15.6
Any metastatic site					
Liver	404	32 (28–37)	8 (5–11)	10	4.8
Retroperitoneal/peritoneal	80	30 (19–40)	3 (0–8)	3	3.6
Other gastrointestinal	100	64 (54–73)	34 (23–46)	35	31.2
Lung	1416	45 (42–48)	13 (11–15)	14	9.6
Lymph node	324	44 (38–50)	14 (9–18)	14	9.6
Bone	975	40 (37–43)	8 (6–10)	9	8.4
Brain	424	25 (21–29)	7 (4–9)	7	3.6
Urogenital	70	73 (62–83)	33 (21–45)	34	21.6
Skin	71	41 (29–52)	7 (0–15)	8	12.0
Soft tissue	101	49 (39–60)	22 (12–32)	22	12.0
Thyroid	79	85 (77–93)	50 (37–63)	53	62.4
Adrenal	141	65 (57–73)	29 (20–37)	31	18.0
Others	105	34 (25–43)	8 (1–15)	9	4.8

n.c. Not computed.
a CI = Confidence interval.

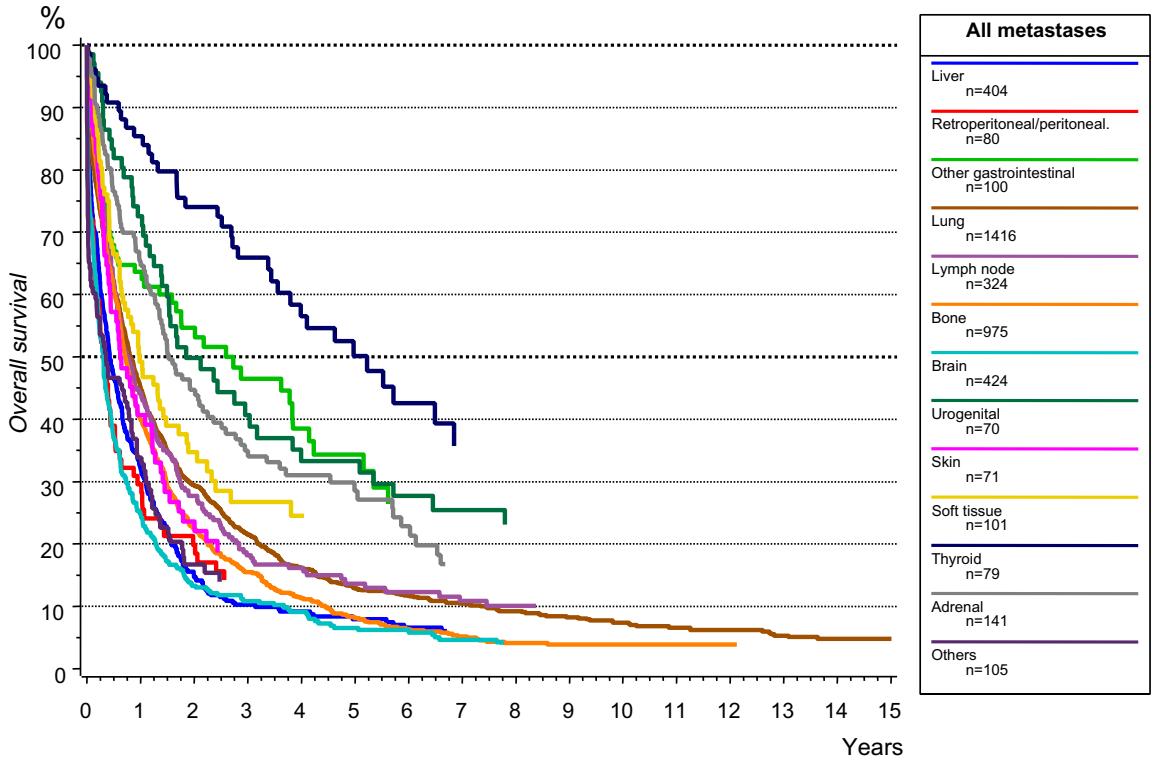


Fig. 3 – Overall survival beginning with diagnosis of any metastasis by metastatic site.

for the patterns of RCC metastases and the survival of patients with metastases at primary diagnosis (M1). The 2000 RCC incidences of 12.4 and 4.7 per 100,000 men and women, respectively, in the Munich region are similar to those in Western Europe and the USA in 2002.[1,11]

The 5 year relative survival in the white US population with kidney cancer is 67%,[12] whereas in the Munich region 77% of RCC patients survive 5 years past their first RCC diagnosis. This remarkable difference corresponds to the difference in the tumour stage-distribution at the initial diagnosis. In the US population, 21% of RCC patients are initially diagnosed with metastases compared to 13% in the Munich region.[12]

One explanation for the lower proportion of M1-patients at the initial diagnosis in Germany could be the widespread use of imaging diagnostics by abdominal ultrasound and computed tomography for screening of common diseases, i.e. in the prostate and vasculature system. In Europe, approximately 46% of patients with RCC are incidentally diagnosed with generally earlier staged tumours.[13,14]

German guidelines for primary staging of RCC metastases recommend abdominal imaging by ultrasound and computed tomography or nuclear magnetic resonance tomography and thoracic imaging by X-ray as standard procedures. Szintigraphy of the bones is only recommended in cases with symptoms of pain or increased serum levels of calcium or alkaline phosphatase. Examination of the central nervous system is only recommended in symptomatic cases.[15]

Although the benefit of systematic aftercare is not proven, German guidelines recommend routinely thoracic and abdominal imaging in close intervals of 3 months in the first 2 years. This approach to staging and aftercare promotes early detection of potentially treatable asymptomatic thoracic and abdominal metastases and late detection of untreatable symptomatic metastases of the bone and brain. Since the progression pattern of RCC metastases depends on the standards in tumour diagnostics, i.e. whether symptomatic or asymptomatic metastases are diagnosed, patterns may vary from country to country.

In the literature there are not many reports about the patterns of RCC metastases in routine care. In the MCR, M1-patients have an average of 1.4 metastases (see Table 2). It is unlikely that the observed proportions of bone and brain metastases (36% and 7%, respectively) reflect symptomatic distant metastases as they should, if staging was done as recommended. Studies have shown similar proportions of patients with brain metastases with a ratio of 7:1 symptomatic to asymptomatic metastases.[16,17] This would suggest that our observed brain metastases are predominantly in asymptomatic patients.

The distribution of metastatic sites is similar in M1- and M0-patients, although M0-patients have fewer (1.2) metastases detected at follow-up (see Table 2). This may indicate that staging at the initial diagnosis is more intensive than in aftercare, leading to a higher proportion of patients with metastases of the lung, the bone and the liver. It is possible that Szintigraphy of the bone at primary diagnostic staging is executed more often than recommended.

Until recently, an intensive aftercare with extended staging activities was not reasonable, due to the limited treatment

Table 4 – Multivariate analysis of prognostic factors predicting death after the first metastasis in patients with metastatic disease at initial diagnosis (M1) and those with metastasis-free interval (M0)

	Number of patients with distant MET, $n = 1169$					
	Primary M1, $n = 505$			Primary M0, $n = 664$		
Factor	HR	P	95%CI	HR	P	95%CI
Age at primary diagnosis (years)		0.4743[a,*]			<.0001[a]	
<50	Ref.			Ref.		
50–59	1.19	0.3126	0.85–1.68	1.00	0.9828	0.75–1.34
60–69	1.02	0.8970	0.73–1.43	1.41	0.0182	1.06–1.86
70–79	1.30	0.1311	0.89–1.91	2.17	<.0001	1.59–2.95
⩾80	1.02	0.9626	0.47–2.21	3.42	<.0001	1.95–6.02
pT Tumour stage		0.0003[a]			0.3854[a,*]	
pT1/2	Ref.			Ref.		
pT3	1.12	0.3926	0.87–1.43	1.06	0.5904	0.87–1.29
pT4	2.36	<.0001	1.54–3.61	1.42	0.1722	0.86–2.34
pN Lymph node stage		<.0001[a]			<.0001[a]	
pN0	Ref.			Ref.		
pN+	1.98	<.0001	1.54–2.54	1.94	<.0001	1.49–2.53
pNX	1.46	0.0114	1.09–1.95	1.19	0.2484	0.89–1.61
Grade		0.0182[a]			0.1008[a,*]	
G1	Ref.			Ref.		
G2	1.35	0.2154	0.84–2.17	1.09	0.5946	0.80–1.49
G3–4	1.77	0.0237	1.08–2.91	1.35	0.0958	0.95–1.91
MET-free interval (months)					0.2502[a,*]	
<12				Ref.		
12 to <24				1.20	0.2007	0.91–1.58
24 to <48				0.90	0.4440	0.70–1.17
⩾48				0.94	0.6351	0.73–1.21
Period of diagnosis of 1st MET		0.5829[a,*]			0.0017[a]	
1978–1987	Ref.			Ref.		
1988–1997	0.96	0.7969	0.72–1.29	0.66	0.0045	0.46–0.88
1998–2001	0.81	0.2398	0.57–1.15	1.00	0.9848	0.75–1.35
Since 2002	0.87	0.5303	0.56–1.34	0.81	0.1934	0.58–1.12

HR hazard ratio.
P Wald test.
CI = Confidence interval.
Ref. = Reference (HR 1.00).
a Linear hypothesis test.
* Not significant with $\alpha = 0.05$.

options available for RCC patients' metastases. Therefore the observed 1.2 metastases per patient may reflect symptomatic metastases which necessitate treatment on the one hand, and the abandonment of further staging activities on the other hand.

In the MCR, 5 year relative survival of M1 patients was 17% and their median survival was 10.8 months. Again, the findings in a US population since 1996 are different: 21% of kidney cancer patients have distant disease at primary diagnosis and their 5 year relative survival is about 10%.[12] In Norway, 8% of all kidney cancer patients with distant disease diagnosed between 1995 and 1999 had a 5 year relative survival of 7.0% and 10.2% for men and women, respectively.[18]

Since the 1990s the only option for a systemic therapy in patients with metastatic disease was immunotherapy using the cytokines interleukin-2 and interferon-α in several regimes. The reported median overall survival in clinical studies varies from 10 to 27 months.[5,19] An analysis based on SEER data reports 5 year RCC-specific survival between 34.2% and 0%, depending on increasing numbers of positive lymph nodes.[20]

The observed median survival of all MCR patients with metastatic disease was 14.4 months and reflects the results of these clinical studies.

The newest targeted therapies with sunitinib, sorafenib and bevacucimab have led to more than 30% of tumour responses, prolonged median progression-free survival and prolonged median survival up to 24 months.[7,9,10,21,22]

It is noteworthy that most randomised clinical studies have a selection bias of patients whose prognosis is likely to be better than in a population-based collective. Patients in clinical studies are younger (<70 or 75 years), in good performance status (ECOG PS 0–1, Karnofsky > 70), without serious heart or vascular comorbidity and without cerebral metastases. The lack of detailed information about treatment regimes in the course of disease in the MCR and the lack of information about the time interval from the initial diagnosis of metastases to death in most clinical studies necessitate the comparison of survival by time periods with adjustment of tumour-specific factors of prognosis.

Multivariate analyses for patients with (M1) or without (M0) metastases at the initial diagnosis showed that in

M1-patients age has no influence on survival, most likely because of the short median survival of metastasised RCC in general. The significant influence of pT category appears to describe a lead time effect. Presumably, tumours with pT4 have grown and stayed undetected for a longer time, resulting in a shorter survival following diagnosis, which is also an effect that is observed with lymph node stage. Additionally, the histologic grade G3–4 shows a significant influence on survival. Interestingly, the period of diagnosis (spanning almost 3 decades) shows no significant influence.

The model for M0-patients shows differences which cannot be completely explained. If metastases are diagnosed symptomatically, the disease should be in such an advanced state that pT category would have little influence. This hypothesis is confirmed in the model. Surprisingly, the metastasis-free interval and the histopathology grade also show no influence. It is possible that the effects of tumour growth are obscured by lymph node stage, which does show significant associations in the model. It is remarkable that age has a strong influence on survival diagnosis of metastasis at follow-up, which was not observed in the model for M1-patients. A significant influence on M0-patient survival was observed for the time period of diagnosis despite its heterogeneity and its insignificance in the first model. Nevertheless, a trend showing continuous improvement over 30 years of RCC management in Bavaria cannot be seen confirming the results of a population-based study in the Netherlands.[6]

In summary, our results can present a baseline incidence and course of metastatic RCC at the onset of wider use of new targeted therapies. These population-based results will provide an important reference for future clinical studies. Furthermore, these data provide evidence that population-oriented cancer registries should consider how such baseline information can be routinely assessed in health care research to provide optimal patient care in developing therapeutic approaches to cancer management.

Conflict of interest statement

None declared.

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