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Better survival in patients with metastasised kidney cancer after nephrectomy: A population-based study in the Netherlands

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ABSTRACT

Aim: Cytoreductive nephrectomy is considered beneficial in patients with metastasised kidney cancer but only a minority of these patients undergo cytoreductive surgery. Factors associated with nephrectomy and the independent effect of nephrectomy on survival were evaluated in this study.

Methods: Patients were selected from the population-based cancer registry and detailed data were retrieved from clinical files. Factors associated with nephrectomy were evaluated by logistic regression analyses. Cox proportional hazard regression analysis was performed to evaluate factors associated with survival; a propensity score reflecting the probability of being treated surgically was included in order to adjust for confounding by indication.

Results: 37.5% of 328 patients diagnosed with metastatic kidney cancer between 1999 and 2005 underwent nephrectomy. Patients with a low performance score, high age, $\geqslant 2$ comorbid conditions, $\geqslant 2$ metastases, low or high BMI, weight loss, elevated lactate dehydrogenase, elevated alkaline phosphatase, female gender and liver or bone metastases were less likely to be treated surgically. Three year survival was 25% and 4% for patients with and without nephrectomy, respectively ($p < 0.001$). After adjustment for other prognostic factors including the propensity score, nephrectomy remained significantly associated with better survival (Hazard ratio: 0.52, 95% Confidence interval: 0.37–0.73).

Conclusions: Even after accounting for prognostic profile, patients still benefit from a nephrectomy; an approximately 50% reduction in mortality was observed. It is, therefore, recommended that patients with metastasised disease receive cytoreductive surgery when there is no contraindication. Trial results on cytoreductive surgery combined with targeted molecular therapeutics are awaited for.

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1. Introduction

In the Netherlands, approximately 2000 patients are diagnosed with kidney cancer each year (www.ikcnet.nl). Kidney cancer has high lethality mostly due to a late clinical presentation. The 5-year relative survival of kidney cancer is 50–55%.[1,2] In case the patients present themselves with metastasised disease, the prognosis is much worse; 5-year survival of 10–20%[2] (http://seer.cancer.gov/). Approximately 30% of all patients with kidney cancer are diagnosed with metastatic disease. Treatment of these patients has shown to be largely unsuccessful. Before the introduction of angiogenesis inhibitors, an EORTC trial[3] and a SWOG trial[4] recommended that patients who are fit enough undergo cytoreductive surgery followed by immunotherapy. It has been shown that this combination has a positive effect on time to progression, prevention of tumour complications and improved response to immunotherapy compared to immunotherapy alone. It is tempting to assume that this also holds for the combination of surgery with angiogenesis inhibitors although there are no solid data yet to support this. Previously we showed that only 40% of the patients with metastasised kidney cancer undergo nephrectomy.[2] In the current population-based study we aim to gain insight into the factors associated with the decision to treat patients with metastasised kidney cancer surgically. Secondly, we evaluate the effect of nephrectomy on survival whilst adjusting for other prognostic factors associated with nephrectomy.

2. Patients and methods

Patients were selected from the population-based cancer registries held by the Comprehensive Cancer Centre East in Nijmegen and the Comprehensive Cancer Centre South in Eindhoven. For this study patients diagnosed with metastasised kidney cancer between 1999 and 2005 were included.

Tumour characteristics, age at diagnosis, gender, primary treatment and vital status were obtained from the cancer registry. Additional data were collected on body mass index (BMI) at time of diagnosis, weight loss at time of diagnosis, family history of kidney cancer, performance status at time of diagnosis, comorbidity and number and location of metastases. Furthermore, several blood parameters at time of diagnosis were obtained: lactate dehydrogenase (LDH), haemoglobin, adjusted calcium, sedimention rate and alkaline phosphatase (AF). All additional clinical information was retrieved by reviewing the medical files and electronic patient databases in all 11 participating hospitals.

All blood parameters were dichotimised according to routinely-used reference values: LDH 1.5 times elevated versus normal, haemoglobin (low versus normal) and AF, adjusted calcium and sedimentation rate (elevated versus normal). Comorbidity was dichotomised into 0–1 comorbid condition versus 2 or more. Metastases were classified as 1 organ involved versus 2 or more. Metastases were grouped by localisation: lymph node, lung, liver, bone and brain. Performance status was defined as high (Karnofsky 80–100%) versus low (70% and lower). BMI was dichotimised into normal (20–30) and abnormal (<20 or higher than 30). Weight loss (at least 5%) prior to diagnosis was defined as yes versus no.

Univariable and multivariable logistic regression analyses were performed to evaluate factors associated with nephrectomy. As several variables had missing data which may lead to biased estimates if not taken into account, we used multiple imputations of missings.[5,6] In summary, it is assumed that the distribution of each variable with missing data can be modelled on the basis of the other variables plus the outcome (nephrectomy or not) with logistic regression modelling if the variable is dichotomous. On the basis of this model posterior predictive values were generated and using the predictive mean matching method, imputations for the missing values were generated and filled in for the missing predictor values. This imputation was repeated 20 times. Variables that were imputed were BMI, weight loss, performance score and comorbidity. The laboratory parameters were not determined in all patients but it was decided not to impute these variables because this information was not available to the clinicians and, therefore, could not have influenced the choice of treatment.

As this study was not randomised, patients who were selected for nephrectomy may not have the same prognostic profile as the patients who were treated differently. To take this into account a propensity score was calculated reflecting the probability of a person undergoing nephrectomy given a set of known covariates.[7] All factors which were univariably associated with nephrectomy were included in a multivariable regression analysis. The propensity of nephrectomy for each patient was obtained based on this model, ranging from 0 to 1 (i.e. the propensity score). The predictive value of the propensity score was estimated using the area under the receiver operating characteristic curve (AUC).

To evaluate the beneficial effect of nephrectomy on survival a Cox proportional hazard regression model was used. Follow-up was defined as the time between date of diagnosis and date of death or February 1st 2007 whichever came first. The crude effect of nephrectomy on survival was estimated and subsequently adjusted for the propensity score. Including this propensity score in the survival model will optimally adjust the bias due to imbalance of prognostic variables associated with nephrectomy. Finally, a complete survival model was made including all variables associated with survival. Factors associated with nephrectomy and, therefore, included in the propensity score model can also independently influence survival. Consequently, these factors were included in the multivariable survival model as well. Statistical analyses were performed using SAS version 9.2.

3. Results

In total 328 patients with metastasised kidney cancer were included in this study. All patients, before and after imputation, and tumour characteristics are reported in Table 1. Mean age at diagnosis was 68 years whilst 13% of all patients were 80 years or older at diagnosis. The majority of patients were male (62%), 24% had a BMI of less than 20 or higher than 30, 63% of the patients had weight loss (⩾5%) prior to diagnosis,

Table 1 – Patient and tumour characteristics.

		Patients *N* (%)	Patients *N* (%) after imputation
Total		328	
Gender	Male	204 (62.2)	
	Female	124 (37.8)	
Mean age at diagnosis		67.6 (sd 11.0)	
Age at diagnosis	<80 years	285 (86.9)	
	⩾80 years	43 (13.1)	
Cigarette smoking	Current/ex-smoker	135 (41.1)	165 (50.2)
	Never smoker	133 (40.6)	163 (49.8)
	Unknown	60 (18.3)	
Body mass index	<20/⩾30	62 (18.9)	80 (24.4)
	20–30	163 (55.8)	248 (75.6)
	Unknown	83 (25.3)	
Weight loss	Yes	136 (41.5)	205 (62.6)
	No	65 (19.8)	123 (37.4)
	Unknown	127 (38.7)	
Performance status	⩾80%	149 (45.4)	195 (59.4)
	<80%	86 (26.2)	133 (40.6)
	Unknown	93 (28.4)	
Positive family history	Yes	4 (1.2)	
	No	133 (40.5)	
	Unknown	191 (58.2)	
Comorbidity	None	77 (23.5)	81 (24.7)
	1 comorbidities	92 (28.0)	98 (29.8)
	⩾2 comorbidities	141 (43.0)	149 (45.5)
	Unknown	18 (5.5)	
Comorbidities (top 5)	Hypertension	123 (37.5)	
	Cardiovascular disease	105 (32.0)	
	Diabetes	55 (16.8)	
	Lung disease	48 (14.6)	
	Cancer	47 (14.3)	
Histology	Clear cell RCC[a]	109 (33.2)	
	Papillary RCC[a]	5 (1.5)	
	Chromofobe RCC[a]	2 (0.6)	
	RCC not otherwise specified	75 (22.9)	
	Sarcomatoid RCC[a]	7 (2.1)	
	Other	6 (1.8)	
	Unknown (only clinically confirmed)	124 (37.8)	
Lateralisation	Left	174 (53.0)	
	Right	151 (46.0)	
	Unknown	3 (0.9)	
Fuhrman grade	1	14 (4.3)	
	2	32 (9.8)	
	3	43 (13.1)	
	4	13 (4.0)	
	Unknown	226 (68.9)	
Tumour size	7 cm or smaller	96 (29.3)	
	Larger than 7 cm	139 (42.4)	
	Unknown	93 (28.4)	
Number of metastasis	1 involved organ	147 (44.8)	
	2 involved organs	119 (36.3)	
	3 or more involved organs	62 (18.9)	

(*continued on next page*)

Table 1 – (*continued*)

		Patients *N* (%)	Patients *N* (%) after imputation
Site of metastasis	Lung	193 (58.8)	
	Liver	69 (21,0)	
	Bone	118 (36.0)	
	Brain	21 (6.4))	
	Lymph node	118 (36.0)	
	Other	56 (17.1)	
Lactate dehydrogenase	Elevated > 1.5 times	35 (10.7)	
	Normal	213 (64.9)	
	Not determined	80 (24.4)	
Haemoglobin	Low	201 (61.3)	
	Normal	110 (33.5)	
	Not determined	17 (5.2)	
Alkaline phosphatase	Elevated	82 (25.0)	
	Normal	154 (47.0)	
	Not determined	92 (28.0)	
Corrected calcium	Elevated	84 (25.6)	
	Normal	86 (26.2)	
	Not determined	158 (48.2)	
Sedimentation rate	Elevated	193 (58.9)	
	Normal	46 (14.0)	
	Not determined	89 (27.1)	
Therapy	No therapy	130 (39.6)	
	Nephrectomy	123 (37.5)	
	Immunotherapy	43 (13.1)	
	Radiotherapy	104 (31.7)	
	Metastectomy	17 (5.2)	
	Angiogenesis inhibitors	7 (2.1)	

[a] RCC: Renal cell carcinoma.

41% had a Karnofsky performance status of less than 80% and 75% had 1 or more comorbid conditions at the time of diagnosis. Only 4 patients reported a positive family history of kidney cancer. Almost 38% of all patients had a tumour which was only clinically confirmed and most tumours were larger than 7 cm at diagnosis (42%).

From the 328, 123 patients underwent nephrectomy. In Table 2 the characteristics of patients in relation with nephrectomy is shown. Women, older patients and patients with weight loss, low performance score, 2 or more comorbid conditions, liver and brain metastases, 2 or more metastases sites, elevated LDH or elevated AF underwent nephrectomy less often. All factors univariably associated with nephrectomy were included in the multivariable logistic regression model which is presented in Table 2 as well. Performance score, liver or bone metastases, number of metastases, comorbidity and age at diagnosis remained significantly associated with nephrectomy. This multivariable model was also used to estimate the propensity score for each patient, i.e. the probability of undergoing a nephrectomy. The AUC of this model was 91% (95% CI: 88–94%) indicating that most variability in the decision of nephrectomy is captured by the model.

In Fig. 1 the survival of all patients with metastasised kidney cancer is presented. The median survival time of all patients was 5.9 months, and patients who were treated surgically clearly showed a better survival rate compared to patients without surgery (log rank test, $p < 0.001$). In Table 3 the results of the univariable and multivariable Cox proportional hazard regression analyses are presented. The crude Hazard Ratio (HR) was 0.31 (95%CI: 0.24–0.40) for patients treated surgically compared to patients treated without surgery. After adjustment for the propensity score, patients with nephrectomy still showed better survival compared to patients with no nephrectomy, although the difference is less pronounced (HR = 0.51 (95%CI: 0.37–0.70)). Finally, all additional variables associated univariably with survival were included in the model. As expected the HR of nephrectomy remained fairly similar (HR = 0.52 (95%CI: 0.37–0.73)) because most of the additional factors are also captured in the propensity score. Other factors significantly associated with survival were weight loss, Karnofsky performance, more than 2 metastases, increased LDH levels and brain metastases.

4. Discussion

At the time of this population-based study, performed before the era of targeted molecular therapies, the mainstay in the treatment of metastatic kidney cancer was cytoreductive nephrectomy and subsequent cytokine-based therapy. This regime was mainly based on findings from two well known EORTC and SWOG trials published by Mickisch et al.[3] and Flanigan et al.[4] in 2001, which showed that cytoreductive

Table 2 – Uni- and multivariable regression models to estimate factors associated with nephrectomy.

	Nephrectomy N_{total} 123 N (%)	No nephrectomy N_{total} 205 N (%)	Univariable OR[a] (95% CI[c])	Multivariable OR[a] (95% CI[c])
Gender				
Male[b]	90 (44.1)	114 (55.9)		
Female	33 (26.6)	91 (73.4)	0.46 (0.29–0.77)	0.98 (0.47–2.05)
Age at diagnosis (per year increase)			0.94 (0.92–0.97)	0.95 (0.92–0.98)
Cigarette smoking				
Never smoker[b]	66 (40.5)	97 (59.5)		
Current/ex-smoker	57 (34.5)	108 (65.5)	0.81 (0.51–1.31)	
Body mass index				
20–30[b]	100 (40.3)	148 (59.7)		
<20/⩾30	23 (28.8)	57 (71.2)	0.62 (0.34–1.11)	
Weight loss				
No[b]	61 (49.6)	62 (50.4)		
Yes	62 (30.2)	143 (69.8)	0.43 (0.24–0.77)	0.49 (0.21–1.14)
Performance status				
⩾80%[b]	117 (60.0)	78 (40.0)		
<80%	6 (4.5)	127 (95.5)	0.03 (0.01–0.09)	0.04 (0.01–0.11)
Comorbidity				
0–1 comorbidities[b]	81 (45.3)	98 (54.7)		
⩾2 comorbidities	41 (27.5)	108 (72.5)	0.46 (0.28–0.74)	0.54 (0.26–1.13)
Number of metastases				
1 involved organ[b]	72 (49.0)	75 (51.0)		
2 involved organs	40 (33.6)	79 (66.4)	0.53 (0.32–0.87)	0.49 (0.23–1.06)
⩾3 involved organs	11 (17.7)	51 (82.3)	0.23 (0.11–0.47)	0.36 (0.13–1.01)
Lung metastasis				
No[b]	53 (39.3)	82 (60.7)		
Yes	70 (36.3)	123 (63.7)	0.88 (0.56–1.39)	
Liver metastasis				
No[b]	112 (43.2)	147 (56.8)		
Yes	11 (15.9)	58 (84.1)	0.25 (0.13–0.50)	0.26 (0.10–0.71)
Bone metastasis				
No[b]	96 (45.7)	114 (54.3)		
Yes	27 (22.9)	91 (77.1)	0.35 (0.21–0.59)	0.24 (0.12–0.50)
Brain metastasis				
No[b]	119 (38.8)	188 (61.2)		
Yes	4 (19.0)	17 (81.0)	0.37 (0.12–1.13)	
Lymph node mestasis				
No[b]	78 (37.1)	132 (62.9)		
Yes	45 (38.1)	73 (61.9)	1.04 (0.66–1.67)	
Lactate dehydrogenase				
Normal[b]	86 (40.4)	127 (59.6)		
Elevated ⩾ 1.5 times	3 (8.6)	32 (91.4)	0.14 (0.04–0.47)	0.23 (0.05–1.08)
Haemoglobin				
Normal[b]	42 (38.2)	68 (61.8)		
Low	73 (36.3)	128 (63.7)	0.92 (0.57–1.49)	
Alkaline phosphatase				
Normal[b]	65 (42.2)	89 (57.8)		
Elevated	18 (22.0)	64 (78.0)	0.39 (0.21–0.71)	1.17 (0.46–2.95)
Corrected calcium				
Normal[b]	37 (43.0)	49 (57.0)		
Elevated	27 (32.1)	57 (67.9)	0.63 (0.34–1.17)	
Sedimentation rate				
Normal[b]	16 (34.8)	30 (65.2)		
Elevated	72 (37.3)	121 (62.7)	1.12 (0.57–2.19)	

[a] OR: odds ratio.
[b] Reference category.
[c] 95% CI: 95% confidence interval.

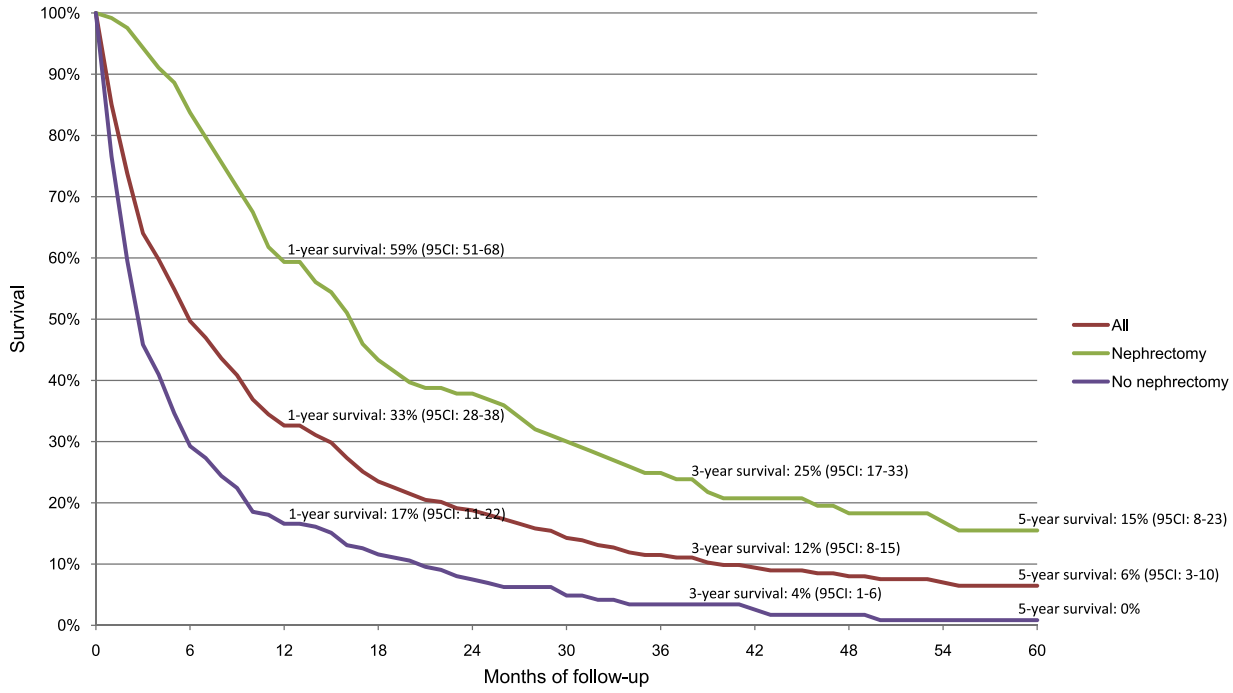

Fig. 1 – Survival of all patients with metastasised kidney cancer and by nephrectomy.

nephrectomy in addition to interferon therapy delayed time to progression and improved survival compared to interferon alone. As an earlier study[2] revealed that in the Netherlands less than 40% of the metastatic kidney cancer patients were treated surgically, we assessed in this population-based study which factors determined the choice to treat patients surgically. Secondly we evaluated the beneficial effect of nephrectomy on survival.

The overall resection rate in this study was 37.5% which is within the range of two other recently performed population-based studies, both based on a SEER cohort, showing resection rates of 30.5%[8] and 44.5%[9], respectively. The pattern of metastatic sites in our study is similar as reported in the earlier studies[10]; the majority of metastases were located in the lung (59%), bone (36%), lymph node (36%) and liver (21%). Poor performance, liver metastases, bone metastases and advanced age at diagnosis were significantly associated with a low probability of nephrectomy. In addition, although not statistically significant, multiple metastases at diagnosis and multiple comorbid conditions appear to be inversely associated with nephrectomy. Poor performance, serious comorbidities that make surgical intervention a high risk, the presence of brain, liver, or bone metastases have all been shown to be associated with a poor prognosis. Therefore, patients exhibiting these clinical features are usually excluded as candidates for cytoreductive nephrectomy. The variation in resection rates between hospitals was limited although there were some hospitals with a fairly low resection rate (minimum 12%) and some hospitals with a high resection rate (maximum 58%). This variation may be due to different patient characteristics but may also be due to different decision making. The Dutch guideline recommends nephrectomy only if the performance of the patient is sufficient. Shuch et al.[11] suggested some nuance by stating that patients with poor performance represent a very heterogenous group of which a subgroup may benefit from cytoreductive nephrectomy; the poor performance group secondary to bone involvement should be considered for nephrectomy whereas the poor performance group secondary to visceral disease may do better with palliative therapy.

Age appeared to be an important independent factor associated with nephrectomy as well. This was also reported by Jeldres and colleagues[8] although in their study the effect of age is probably confounded by performance status and comorbidity, as information on these factors was not available. Kader and colleagues[12] performed a study including patients with metastatic renal cell carcinoma treated with cytoreductive nephrectomy and compared the survival benefit of the elderly ($\geqslant$75 years) and young patients (<75 years). Median survival in both groups was similar but the peri-operative mortality and morbidity were higher in the oldest group. This suggests that the prognosis amongst elderly is comparable to the younger patients as long as they survive the surgery. For that reason, age alone should not be a criterion whether or not to treat patients with cytoreductive surgery.

Second goal of this study was to evaluate the effect of nephrectomy on survival. The benefit of the cytoreductive nephrectomy was already demonstrated in 2001 by two randomised controlled trials[3,4] mentioned before and consequently the recommended therapy for metastatic renal cell carcinoma patients has consisted of cytoreductive nephrectomy followed by INF-α or interleukin (IL-2) in patients fit enough. An important limitation of trials is that included patients are often highly selected (e.g. no comorbidity, relatively young age at diagnosis, good performance) and not representative for the general patient population. The survival benefit may be less or absent in unselected patients. Next to these clinical trials, only some small clinical case series have

Table 3 – Cox Proportional Hazards regression analyses including nephrectomy, propensity score and other prognostic variables.

	Univariable HR[a] (95% CI[c])	HR[a] nephrectomy adjusted for propensity score (95% CI[c])	Multivariable HR[a] (95% CI[c])
Nephrectomy			
No[b]			
Yes	0.31 (0.24–0.40)	0.51 (0.37–0.70)	0.52 (0.37–0.73)
Propensity score (continuous)	0.14 (0.10–0.21)	0.28 (0.17–0.46)	0.77 (0.36–1.64)
Gender			
Male[b]			
Female	1.27 (1.00–1.60)		
Age at diagnosis (per year increase)	1.01 (1.00–1.03)		
Cigarette smoking			
Never smoker[b]			
Current/ex-smoker	1.17 (0.93–1.47)		
Body mass index			
20–30[b]			
<20/⩾30	1.01 (0.78–1.31)		
Weight loss			
No[b]			
Yes	1.97 (1.54–2.51)		1.65 (1.28–2.15)
Performance status			
⩾80%[b]			
<80%	3.00 (2.36–3.81)		1.67 (1.15–2.45)
Comorbidity			
0–1 comorbidities[b]			
⩾2 comorbidities	1.09 (0.86–1.37)		
Number of metastases			
1 involved organ[b]			
2 involved organs	1.50 (1.16–1.94)		1.39 (1.05–1.83)
⩾3 involved organs	2.11 (1.54–2.89)		1.72 (1.19–2.48)
Lung metastasis			
No[b]			
Yes	1.18 (0.93–1.49)		
Liver metastasis			
No[b]			
Yes	1.88 (1.43–2.48)		
Bone metastasis			
No[b]			
Yes	1.35 (1.06–1.71)		
Brain metastasis			1.73 (1.07–2.79)
No[b]			
Yes	2.28 (1.45–3.59)		
Lymph node mestasis			
No[b]			
Yes	1.14 (0.90–1.44)		
Lactate dehydrogenase			
Normal[b]			
Elevated ⩾ 1.5 times	2.81 (1.95–4.05)		1.85 (1.23–2.78)
Alkaline phosphatase			
Normal[b]			
Elevated	1.92 (1.45–2.54)		
Sedimentation rate			
Normal[b]			
Elevated	1.50 (1.05–2.13)		

(*continued on next page*)

Table 3 – (*continued*)

	Univariable HR[a] (95% CI[c])	HR[a] nephrectomy adjusted for propensity score (95% CI[c])	Multivariable HR[a] (95% CI[c])
Haemoglobin			
Normal[b]			
Low	1.34 (1.04–1.72)		
Corrected calcium			
Normal[b]			
Elevated	1.43 (1.04–1.96)		
Lateralisation			
Left[b]			
Right	0.88 (0.70–1.10)		
Tumour size			
<7 cm[b]			
⩾7 cm	1.05 (0.83–1.33)		
Fuhrman grade			
1[b]			
2	1.03 (0.49–2.18)		
3	1.42 (0.70–2.89)		
4	1.76 (0.76–4.09)		

[a] HR: hazard ratio.
[b] Reference category.
[c] 95% CI: 95% confidence interval.

been performed evaluating the role of nephrectomy and results from these studies are inconsistent which may be due to the small number of patients, their retrospective nature and lack of adjustment for other prognostic factors.[13,14] It is, therefore, important to confirm the beneficial effect of nephrectomy in a population-based setting. In our population-based study the multivariable Cox proportional hazards regression analysis showed a HR of 0.52 (95% CI: 0.37–0.73) for patients with nephrectomy versus no nephrectomy which corresponds with an almost two-fold increased mortality in patients without nephrectomy. This HR was adjusted for the favourable prognostic profile associated with nephrectomy by using the propensity score reflecting the probability of being treated surgically. It was shown by Rosenbaum and Rubin[7] that this propensity score leads to strongly ignorable non-randomised treatment assignment, i.e. it will remove most confounding by indication. As far as we know, only one other population-based study has evaluated the effect of nephrectomy on survival of patients with metastatic kidney cancer.[9] In that study a 2.5-fold increased mortality in patients without nephrectomy was found. However, they had only adjusted the effect of nephrectomy for age and the favourable prognostic profile associated with nephrectomy was not taken into account.

Next to nephrectomy, weight loss prior to diagnosis, performance score, 2 or more metastases at diagnosis, the presence of brain metastases and elevated LDH levels were associated with decreased survival. These results are largely in line with findings from other studies.[11,15–27]

In the period this study was executed better understanding of the underlying biology of metastatic kidney cancer has led to the introduction of novel systemic therapeutic agents and thereby a shift in the treatment paradigm of kidney cancer in general and metastatic kidney cancer as well. These targeted molecular therapies include angiogenesis inhibitors, targeting the vascular endothelial growth factor (VEGF) pathway by neutralising antibodies (bevazuzimab) or receptor tyrosine kinase inhibitors (sunitinib, sorafenib) or mammalian target of rapamycin inhibitors (temsirolimus, everolimus). Several randomised trials have demonstrated that these novel agents have a beneficial effect on progression free and overall survival compared to interferon-alpha as the first-line treatment.[28–33] In these trials the majority of patients underwent a cytoreductive nephrectomy prior to the targeted therapy. Therefore, the effect of the cytoreductive surgery could not be evaluated anymore. The role and sequence of cytoreductive nephrectomy in the new era of targeted therapy are currently under investigation.[34] In the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA; NCT00930033) which started recently, patients with metastatic kidney cancer with a good performance without prior systemic therapy of surgery are randomised into nephrectomy followed by sunitinib or sunitinib alone (http://clinicaltrials.gov/ct2/show/nct00930033). Very limited data are available from retrospective studies suggesting a beneficial effect of prior nephrectomy[35] (Choueiri et al. 2010 ASCO, Urogenitourinary Cancer Symposium). Furthermore, the timing of the nephrectomy may be important as well. The recently started EORTC trial (30073) evaluates immediate (arm I: nephrectomy and after 4 weeks start with sunitinib malate) versus deferred nephrectomy (arm II: sunitinib malate once daily on days 1–18 and this is repeated every 6 weeks for 3 courses and after completion undergo nephrectomy) in patients with metastatic renal cell carcinoma on survival. Giving sunitinib malate before nephrectomy may reduce the tumour size and reduce the amount of normal tissue that

needs to be removed during surgery. Giving sunitinib malate after surgery may kill any tumour cells that remain after surgery. It is unclear which of these two approaches is more beneficial. In conclusion, this is the first population-based study able to distinguish the effect of nephrectomy and prognostic factors associated with nephrectomy on survival. A clear beneficial effect was found for patients who underwent nephrectomy. We recommend that nephrectomy should always be considered in patients with metastasised kidney cancer who are fit enough for surgery.

Conflict of interest statement

None declared.

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