Original Article

Local survival outcomes in metastatic renal cell carcinoma

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Abstract

A quarter of patients who develop renal cell carcinoma will have metastatic disease at presentation. The role of cytoreductive surgery in these patients is a topic of debate.

The aim of this study was to analyse survival outcomes of patients treated in Malta who did and did not receive a nephrectomy.

Data was gathered retrospectively from the Malta Cancer Registry and Mortality Data at the Department of Health Information, records of multidisciplinary team meetings held within the urology department at Mater Dei Hospital, hospital imaging and patient records. Data gathered included: patient demographics, date of diagnosis, TNM staging, tumour histology, Fuhrman grade, time to treatment and modality of treatment.
Exclusions included:

- Localized disease relapsing after surgery
- Non-renal cell histological subtypes
- Presence of metastasis at diagnosis not certain
- Concomitant primary tumours

77 patients diagnosed over 5 years between 04.03.2005 and 13.2.2009 were included. The age at presentation ranged from 30 to 88 years, with a median age of 67 years. 11 were incidental findings and 47 were symptomatic. The most prevalent symptoms were abdominal pain and gross haematuria.

Five-year cancer specific survival in patients who received a nephrectomy was significantly better at 65%, compared to patients who did not undergo surgery (32%) P value <0.05, CI 95%. These results where compared favourably with SEER data outcomes

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Keywords

Renal cell cancer, cytoreductive nephrectomy, cancer specific survival.

Introduction

Renal cell carcinoma (RCC) is one of the ten most common malignancy in both men and women. The American Cancer Society estimates that 62,700 new cases of renal cell carcinoma (39,650 in

men and 23,050 in women) will be diagnosed in 2016 in the USA, with 14,240 people (9,240 men and 5,000 women) dying from this disease. [1] Local data from the European Cancer Observatory for 2012 cites a Maltese incidence and mortality from RCC of 57 and 27 per 100, 000 population (age standardised) respectively.[2]

The incidence of RCC has increased over the last decade, and although there has been a definitive stage migration to low stage disease, this being attributed to increasing use of cross sectional imaging and incidental diagnosis of RCC , up to 25% of cases are metastatic at diagnosis.[3] The prognosis in these cases is dismal with the American Joint Committee on Cancer quoting only an 8% five-year overall survival for stage IV RCC.[4]

Faced with these poor outcomes and paucity of oncological alternative therapies, the urological community investigated the benefit of cytoreductive nephrectomy in the presence of distant metastases, and showed a survival benefit when combined with interferon therapy.[5-6] More recently, the development of targeted therapies has led to the substitution of interferon therapy by these drugs in view of their superior efficacy and adverse effect profile. [7] In the local setting, sunitinib (Sutent®), a tyrosine kinase inhibitor, has been the sole agent in use for many years, although more recently everolimus has also been introduced as second line therapy for patients progressing on sunitinib or first line therapy for poor prognosis metastatic cases. The role of cytoreductive nephrectomy in combination with these new agents is still a controversial issue.[8-9]

In this retrospective, non-randomised observational study we compared survival outcomes in a local population of patients with metastatic renal cell carcinoma receiving Sunitinib treatment with or without nephrectomy.

Method

The aims of this study where to analyse cancer specific survival in patients with metastatic RCC in Mater Dei Hospital Urology Unit, compare outcomes between patients having cytoreductive nephrectomy with patients receiving oncological management with sunitinib monotherapy, analyse survival in patients stratified according to MSKCC prognostic groups, and compare these results with National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program database outcomes.

All patients presenting with metastatic renal cell carcinoma to the Urology Unit at Mater Dei Hospital between 04.03.2005 and 13.2.2009 were retrospectively considered for inclusion. The diagnosis was based on radiological investigations. Histological confirmation of cancer types was not mandatory in patients who did not receive a nephrectomy in view of the high diagnostic specificity and sensitivity of cross sectional imaging in the diagnosis of solid or complex cystic renal masses.

Patients were excluded if their primary disease was a non-renal cell kidney cancer, the presence of distant metastases was in doubt at time of diagnosis, the metastatic progression occurred in the context of localised disease at diagnosis that relapsed at a distant site following surgery with curative intent or the presence of other primary tumours prior to or following diagnosis of renal cell cancer. Patients were also excluded if they did not receive at least one dose of sunitinib adjuvant therapy.

Data was gathered retrospectively from the Malta Cancer Registry and Mortality Data at the Department of Health Information, records of multidisciplinary team meetings held within the Urology department at Mater Dei Hospital, hospital imaging and patient records. Mortality data was corroborated by death certification data obtained from the National Cancer Registry to minimise inaccuracy.

Data gathered included: patient demographics, date of diagnosis, TNM staging, tumour histology, Fuhrman grade, time to treatment and modality of treatment.

The patients were risk stratified according to the revised Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk groups for metastatic renal cancer. These represent a revision of the original Motzer criteria, [10] updated by Heng *et al* in 2009 to reflect the introduction of targeted therapy in the management of metastatic kidney cancer.[11] These have been externally validated in an independent large series.[12]

The prognostic factors that are included in this model include; Karnofsky performance score <80%, time to treatment <1 year, anaemia, hypercalcaemia, neutrophilia and thrombocytosis. Patients were risk stratified into three groups as follows; good prognosis if 0 factors, intermediate prognosis if 1 – 2 factors, poor prognosis if >2

factors as in the original paper by Heng *et al*.

Long term cancer specific survival outcome was compared between two patient groups, those who received cytoreductive nephrectomy and those who did not. Cancer specific survival was also investigated in a subgroup analysis per MSKCC prognostic group stratification. Survival between the two groups was documented via Kaplan Meier survival curves, with a p value of <0.05 taken to represent significance.

Results

77 patients satisfied the inclusion criteria. The study period selected allowed for the analysis of long term survival data in this patient population, with the shortest assessment interval (to death or ongoing survival) being 3.5 years. The majority of patients enrolled were male, 53, as opposed to 24 female patients. The median age at presentation was 67 years with a range from 30 years to 88 years.

14% of cases were incidental diagnoses, whilst 61% of patients presented with symptoms related to local or metastatic disease. In 25% of cases the method of presentation was not available. The most common symptoms at presentation where abdominal or loin pain (21%), gross haematuria (19%), lung (13%) or spinal (11%) symptoms. (Figure 1).

The vast majority of cases presented with T3 or T4 tumours at diagnosis, as per UICC International Union Against Cancer, 7th Edition.[13] (Figure 2). 47 were clinically node negative at presentation, whilst 29 cases had radiological evidence of regional lymph node metastases, lymph node status was not documented in one patient. All patients had radiological evidence of distant metastases at time of diagnosis, thus being classified as TNM stage IV.

***Figure 1**: Presenting features in symptomatic cases*

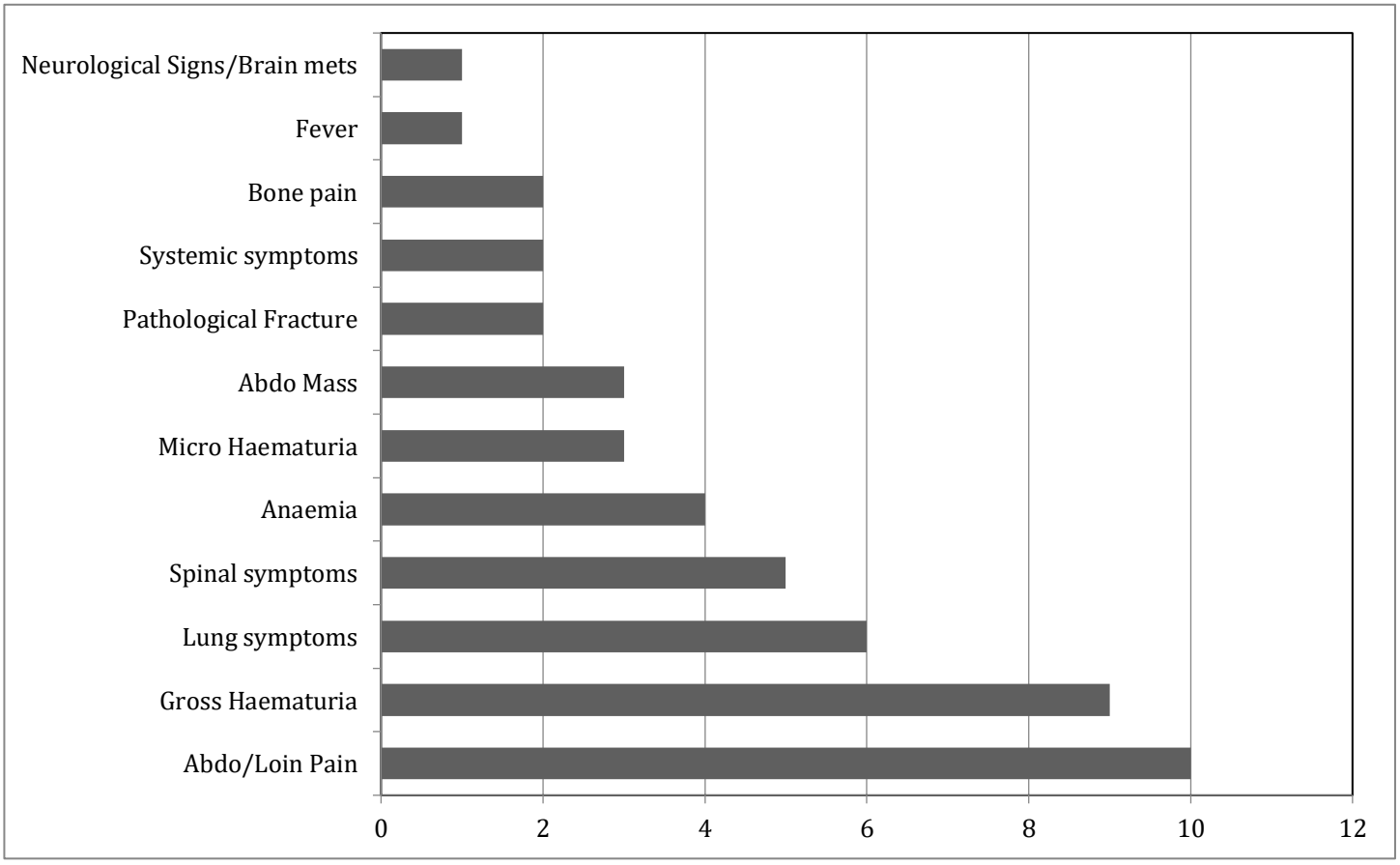


***Figure 2**: Local Tumour stage at diagnosis.*

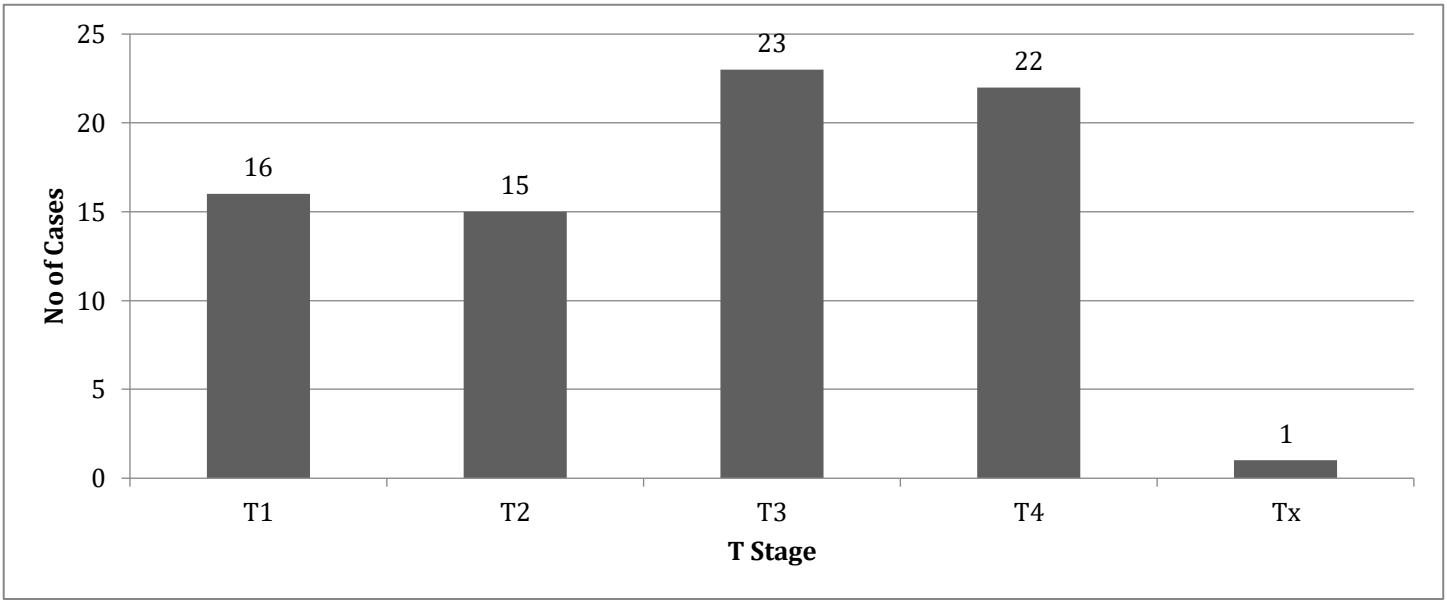


***Figure 3**: Kaplan Meier Curves showing improved cancer survival in nephrectomy group.*

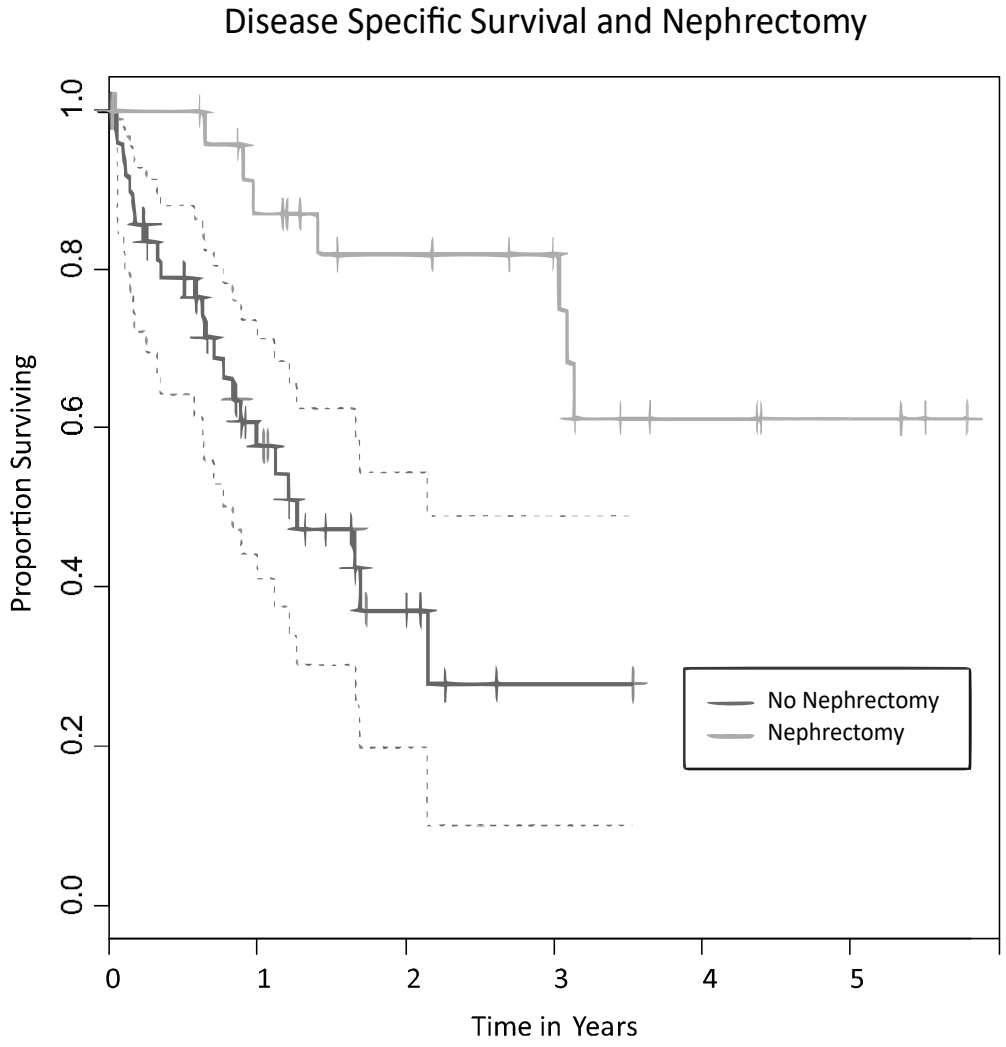
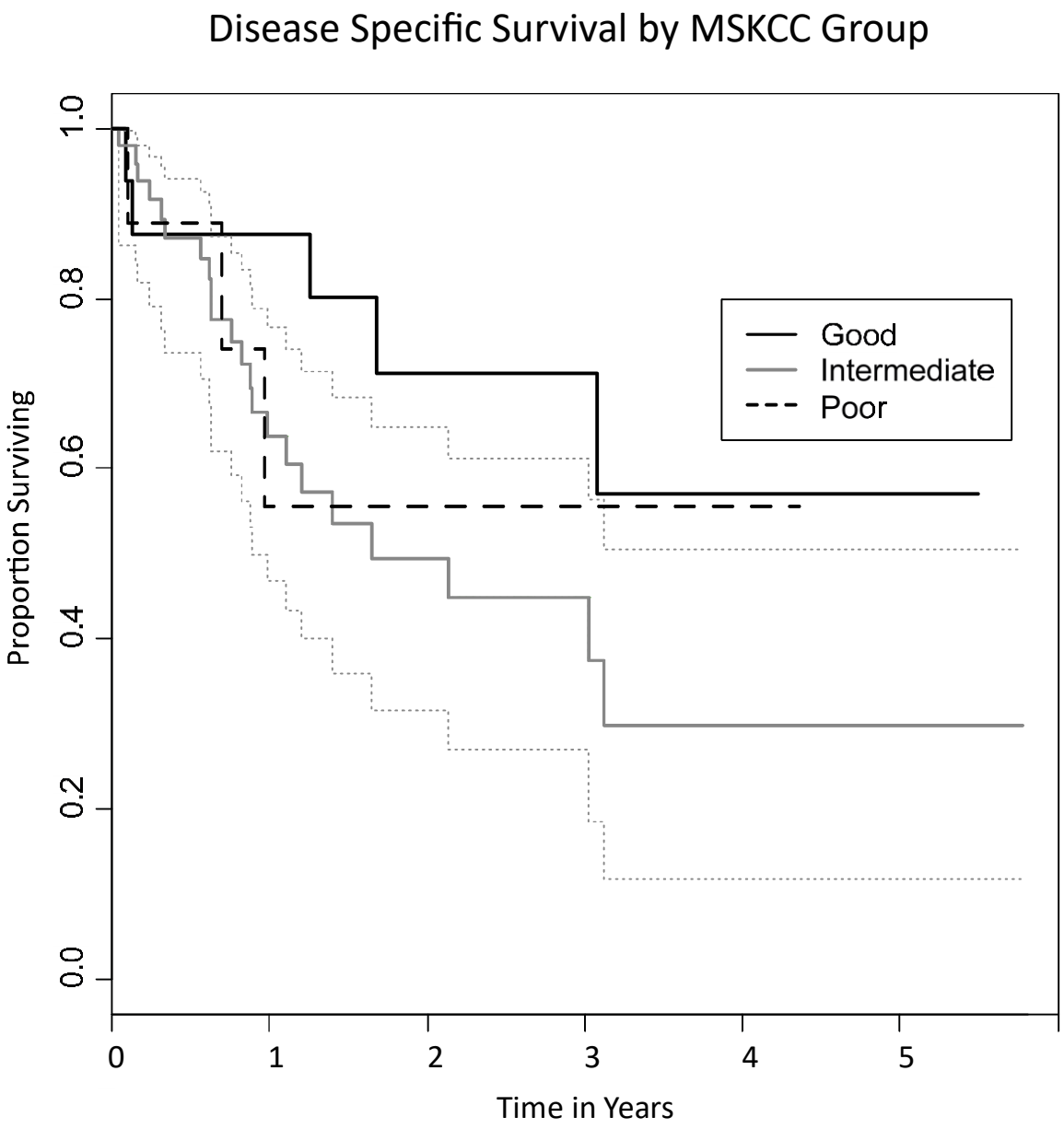


***Figure 4**: Kaplan Meier curve for MSKCC good, intermediate and poor prognosis groups*



Histological subtype was known in only 40% in view of the fact that most patients did not have radical surgery or biopsy of metastatic lesions but diagnosis relied on imaging. In those patients where histology subtype was known, clear cell RCC was the predominant type in keeping with RCC epidemiological patterns (clear cell 27 cases, papillary 2 cases, chromophobe 2 cases).

25 (32.5%) patients underwent cytoreductive open radical nephrectomy during the study period. 45 patients (58%) had passed away at time of censoring (18/8/2015).

Five-year specific survival in patients who received a nephrectomy was significantly better at 65%, compared to patients who did not undergo surgery (32%) P value <0.05, CI 95% as showing in Figure 3.

Subgroup analysis with stratification per MSKCC prognostic risk factors was performed. 17 patients were classified as good prognosis, 49 were considered to have an intermediate prognosis and 10 patients were included into the poor prognosis group. Insufficient data prevented accurate stratification in one patient who was excluded from subgroup analysis.

Five-year survival data showed a significant

difference between the good prognosis and intermediate prognosis groups with a trend towards a poorer outcome in the intermediate group. The poor prognosis group had better long term outcome than the intermediate group, however this is likely to represent an outlying and unrepresentative result in view of the small number of patients in this group. These results are showed graphically in Figure 4.

These results where compared favourably with SEER data outcomes,[15-16] as shown in Tables 1 and 2.

Discussion

In modern day urology, almost one third of clear cell renal cell cancers (the predominant histological subtype of renal cell carcinoma) present with locally advanced or metastatic disease.[17] Given the relatively high incidence of renal cell cancer, the urological and oncological community is faced with the difficult management of a significant number of patients whose disease has a poor long term outcome despite aggressive multimodality management with surgery and an ever expanding armamentarium of targeted therapies.

This aggressive approach is still a topic of debate, as only retrospective non-comparative data exists for cytoreductive nephrectomy in combination with modern targeted therapies. The pioneering work which explored the role of radical surgery in the presence of metastatic disease was performed in the era of immunotherapy prior to the introduction of targeted biological agents. A meta-analysis of these studies, published in the *Lancet Oncology* in 2014, did show an increased long term survival in patients treated with surgery and immunotherapy compared to patients who received immunotherapy alone.[18]

***Table 1**: Cancer specific survival for local patient cohort compared to SEER database data one, two and three years.*

	Malta (2005-2009)		**SEER Database (2006-2009)**	
	Nephrectomy	No Nephrectomy	Nephrectomy	No Nephrectomy
1 year	75.2%	51.2%	70.6%	45.1%
2 years	71%	34.3%	52.2%	27.9%
3 years	65.3%	26.8%	41.7%	21.7%

***Table 2:** Cancer specific survival statistics at 5 years, local and US data.*

MSKCC Prognosis	**Malta (2005-2009)**	**SEER Database (2006-2009)**
Good	57%	36.2%
Intermediate	32%	25.1%
Poor	54%	9.1%

***Table 3**: Published literature investigating role of cytoreductive nephrectomy in combination with targeted therapies in the setting of metastatic renal cell cancer.*

Study (period studied)	Patients, n; CN, no CN	Median OS with CN, months	Median OS without CN, months	Statistically significant patient dispositions in favour of CN ($p \leq 0.001$ to $p < 0.05$)
Retrospective, multi-institutional (2004–2008); Choueiri et al., 2011 [20]	314; 201, 113	19.8	9.4	• Younger age • Better KPS • One metastatic site • Less calcium
Retrospective, SEER (1993–2010); Conti et al., 2014 [21]	20 104; 6915, 13 189	19	4	• Younger age • Male • White
Retrospective, IMDC (2005–2013); Heng et al., 2014 [9]	1658; 982, 676	20.6	9.6	• Better IMDC risk • Less non–clear cell RCC • Fewer bone metastases • Fewer liver metastases
Retrospective, multi-institutional (2006–2011); Bamias et al., 2014 [22]	186; 109, 18	23.9	9.0	• Younger age • Better PS • Less neutrophilia • Lower LDH
Retrospective, SEER (2005–2009); Abern et al., 2014 [23]	2382; 1521, 861	20	6	• Younger age • Male • White
Retrospective, SEER non-clear cell RCC only (2000–2009); Aizer et al., 2014 [24]	591; 377, 214	14	6	• Younger age • Male • White
Retrospective, multi-institutional (1999–2009); Mathieu et al., 2015 [25]	351; 298, 53	38.1	16.4	• Better MSKCC risk • Better ECOG score
Retrospective population-based registry, propensity score matching (2008–2010); De Groot et al, in press [26]	227; 74, 151	17.9	8.8	• T stage <T3/T4 • One metastatic site • Fewer bone metastases
Retrospective, National Cancer Data Base, treated with targeted therapy (2006–2013); Hanna et al, in press [27]	15 390; 5374, 10 016	17.1	7.7	• Younger age • Privately insured • Academic centre • Lower T stage • cN0

Recently this treatment paradigm was adopted by urologists and oncologists and applied to metastatic patients who are treated with targeted therapies which have replaced immunotherapy in modern practice. The evidence base for this approach is not extensive, with no randomised controlled trials to support such an approach to date. Whilst awaiting the results of two randomised trials that are designed to end to this debate, CARMENA (ClinicalTrials.gov identifier NCT00930033) and SURTIME (ClinicalTrials.gov identifier NCT01099423), the European Association of Urology recommends surgery in highly selected patients with good performance status, large primary tumours and low metastatic volume.[17,19]

This approach to metastatic renal cell cancer introduces a heavy selection bias with retrospective studies, with fitter patients with less aggressive disease receiving surgery, whilst those who have a poorer performance status or heavy metastatic load receiving oncological treatment as monotherapy. This inherent flaw cannot obviate the fact that all the retrospective studies published to date have shown an overall survival advantage with surgery in addition to biological agents. (Table 3).

This trend is also evident in our cohort of local patients in which patients who received a nephrectomy had a better long term cancer specific survival than those patients who did not. This is the most important take home message obtained from this retrospective review.

Subgroup analysis with patient stratified according to MSKCC prognostic groups showed some unexpected results with the poor prognosis group of patients doing better than the intermediate risk group. This can probably be attributed to the small number of patients in this group which has resulted in a surprising good outcome.

Compared to SEER data the outcomes in our local cohort of patients compare favourably or significantly better, in all three risk groups but especially in the subgroup who underwent nephrectomy. Again, the vastly superior outcome in the poor prognosis group should not be taken as a true reflection of clinical outcomes in this very small group of patients as already discussed.

The primary tumour accounted for >90% of tumour burden in 55 patients (71.4%), this is an important point as it is likely that a cytoreductive nephrectomy would benefit patients who have most of their tumour mass limited to the kidney. 50 patients (65%) presented with metastases above the diaphragm, this is also relevant as some authorities would not offer debulking nephrectomy in patients with disease above the diaphragm as this is thought to be a very poor prognostic factor with limited benefit being obtained with a surgical approach.[14]

Being the only urology unit in the country, follow up is mostly complete with no patients lost to follow up because of migration. Patients were followed up for an adequate period of > 5 years as is mandatory in oncology studies where survival is the outcome.

Limitations include those inherent to a retrospective audit, including incomplete data, reliance on potentially inaccurate medical notes and bias. Data on overall survival is not presented, and this could reflect real life outcomes in a more meaningful way than cancer specific survival.

Conclusions

Cytoreductive nephrectomy in the presence of metastatic renal cell cancer does seem to offer a survival advantage as demonstrated in this study and other retrospective non-randomised trials. The results from two ongoing large multi-centre randomised controlled studies which are addressing this issue are eagerly awaited.

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