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Management and outcomes of patients with renal medullary carcinoma: a multicentre collaborative study

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Abstract

Objective—To describe the management strategies and outcomes of patients with renal medullary carcinoma (RMC) and characterise predictors of overall survival (OS).

Patients and Methods—RMC is a rare and aggressive malignancy that afflicts young patients with sickle cell trait; there are limited data on management to date. This is a study of patients with RMC who were treated in 2000–2015 at eight academic institutions in North America and France. The Kaplan–Meier method was used to estimate OS, measured from initial RMC diagnosis to date of death. Cox regression analysis was used to determine predictors of OS.

Results—In all, 52 patients (37 males) were identified. The median (range) age at diagnosis was 28 (9–48) years and 49 patients (94%) had stage III/IV. The median OS for all patients was 13.0 months and 38 patients (75%) had nephrectomy. Patients who underwent nephrectomy had superior OS compared to patients who were treated with systemic therapy only (median OS 16.4 vs 7.0 months, $P < 0.001$). In all, 45 patients received chemotherapy and 13 (29%) had an objective response; 28 patients received targeted therapies, with 8-week median therapy duration and no objective responses. Only seven patients (13%) survived for >24 months.

Conclusions—RMC carries a poor prognosis. Chemotherapy provides palliation and remains the mainstay of therapy, but <20% of patients survive for >24 months, underscoring the need to develop more effective therapy for this rare tumour. In this study, nephrectomy was associated with improved OS.

Keywords

kidney cancer; nephrectomy; renal cell carcinoma; renal medullary carcinoma (RMC); #KidneyCancer; #KCSM

Introduction

Renal medullary carcinoma (RMC) is a highly aggressive malignancy arising from the collecting duct epithelium of the kidney. It was first described by Davis et al. [1] in 1995 as the ‘seventh sickle cell nephropathy’, afflicting mostly young patients of African descent with sickle cell trait. However, while sickle cell trait is most commonly carried in those of African descent, it can also occur in Hispanics and Caucasians, particularly those of southern European descent. To date, most reports suggest a median overall survival (OS) of 4–5 months [2].

The pathogenesis of RMC is not completely understood. It has been hypothesised to be related to chronic medullary hypoxia causing up-regulation of the hypoxia-inducible factor pathway, leading to tumour neovascularisation; however, this is not a comprehensive explanation of the pathogenesis [3–5]. RMC typically presents in the second and third decades of life, with male preponderance and primarily right-sided laterality. Most patients present with haematuria or flank pain, and many of these have systemic symptoms such as weight loss [2]. The vast majority of patients present with metastatic disease [6]. RMC generally has a rapidly progressive course. Lymphovascular spread is common with direct invasion to renal sinus veins, regional lymph nodes, and retroperitoneum [7].

Radiographically, tumours arise centrally and demonstrate an infiltrative pattern, distinctly different in appearance from the exophytic peripheral masses of clear-cell RCC [8,9].

Pathologically, these tumours are characterised by large locally advanced renal tumours that frequently show extrarenal extension at the time of presentation. Key pathological features include stromal desmoplasia, prominent nucleoli, and frequent cytoplasmic inclusions resembling rhabdoid tumour cells [10–13]. The diagnosis of RMC is confirmed by demonstrating loss of SMARCB1 (INI1) nuclear staining.

As RMC is extremely rare, there is paucity of data on the optimal management of patients who present with advanced disease. Only small series exist on the treatment of RMC; the largest single-centre data is the report of 34 patients by Davis et al. [1] in 1995. Iacovelli et al. [2] reported on 165 patients pooled from 18 years of literature, but most single-centre treatment data included less than four patients, and individual patient data were not reported. Reported treatment regimens include various cytotoxic chemotherapy and targeted therapy regimens, but the role of nephrectomy to date has been unclear. Topoisomerase overexpression has been evaluated, and based on this rationale, doxorubicin has been used in combination with other chemotherapy agents [14,15]. Platinum-based regimens are also

frequently used as they have shown improvement in survival [16]. However, the long-term outcome of patients with RMC remains poor. We report the largest experience to date of 52 patients with RMC treated at eight institutions. Our objectives were to study the clinical presentation, treatment methods, outcomes, and predictors of survival.

Patients and Methods

We conducted this retrospective, multicentre study after Institutional Review Board approval was obtained. A combined de-identified secure database was constructed and all patients with confirmed RMC diagnosed and treated from 2000 to 2015 at eight participating academic institutions in North America and France were included in this study.

Clinical and Pathological Characteristics

Clinical, imaging, and pathological data were available for 52 patients. Clinical information collected at presentation included age, gender, race, symptomatology, presence of haemoglobinopathy, tumour laterality, renal primary tumour size, clinical stage (American Joint Committee on Cancer), Eastern Cooperative Oncology Group performance status (ECOG PS), number of organs involved with metastatic disease, metastatic sites, and baseline laboratory studies. Data on radical or partial nephrectomy and timing of surgery was collected. Information on imaging including full staging evaluation of CT chest, abdomen, and pelvis, as well as bone scan and brain MRI when indicated, was collected. Pathological information included histology from biopsy or nephrectomy material (when nephrectomy was performed), and pathological T and N stage, when available. All available pathology slides were reviewed by genitourinary pathologists at each participating institution. All patients had confirmed RMC histology. Information on systemic therapy was collected including its timing (pre- vs postoperative), duration of therapy, best response, and regimens used. Date of death or last follow-up was collected for survival analysis.

Statistical Methods

Descriptive statistics were used for continuous variables (median, range). OS was measured in months from time of diagnosis until death or last follow-up. Patients who were alive at their last contact were censored on that date. Kaplan–Meier plots were used to estimate OS times [17]. The log-rank test and Cox regression analysis models were used to evaluate the association of co-variables with OS [18,19]. Variables with a *P* value < 0.1 were included in the multivariable analysis. *P* values in the multivariable analysis of <0.05 were considered statistically significant.

Results

Patient Characteristics at Presentation

In all, 52 patients (47 Black, 4 White, and 1 Hispanic non-White by self-report) were identified. The median (range) age at diagnosis was 28 (9–48) years and 37 patients (71%) were male. In all, 51 patients had sickle cell trait, and one patient had sickle β thalassaemia. In all, 66% of patients presented with haematuria and/or flank pain and 50% presented with constitutional symptoms, most frequently unintentional weight loss, followed by night

sweats; 20% of patients presented with cough, shortness of breath, or abdominal pain related to metastatic disease. In all, 36 patients (69%) had right-sided tumours and the median (range) tumour size at presentation was 6.0 (3.4–11.4) cm. In all, 14 patients (27%) presented with Stage III disease, and 35 patients (67%) presented with Stage IV (distant metastatic) disease. Of those that presented with metastatic disease, one patient was in the ‘good risk’ category by Memorial Sloan-Kettering Cancer Center (MSKCC) risk score, 17 (49%) were in the ‘intermediate risk’ category, and 17 (49%) were in the ‘poor risk’ category. In all, 44 patients (85%) had radiographic lymph node involvement at presentation (>1 cm in the short axis), most commonly in the retroperitoneum. Other common sites of metastatic disease included the lungs (46%), liver (15%), and bone (15%). No patients had brain metastases at presentation. In all, 32 patients (62%) had an ECOG PS of 0–1, and 20 patients (38%) had an ECOG PS of 2–3. Additional details on demographics and presentation are given in Table 1.

Pathology and Surgery

In all, 25 patients (48%) had renal mass biopsy as part of their initial evaluation. All patients had pathological confirmation of RMC on either biopsy or nephrectomy specimen and 38 patients (73%) underwent nephrectomy during their treatment course (37 radical nephrectomies and one partial nephrectomy). Eight of the patients who underwent nephrectomy received preoperative systemic chemotherapy, whereas 30 patients underwent upfront nephrectomy before any systemic therapy. Seven patients had pT1 disease, 29 patients had pT3 or pT4 disease, and 24 patients had pathological confirmation of disease in lymph nodes. Additional pathology details are given in Table 1.

Survival

The median follow-up time was 34.4 months (95% CI: 27.5–N/A) for the entire cohort, and the median OS was 13.0 months (95% CI: 9.0–17.9; range 0.2–45.2). The 12-month OS rate was 53% (95% CI: 40–69), and the 24-month OS rate was 17% (95% CI: 9–33). The log-rank test did not show a significant difference in OS by subgroup variables of age, gender, presence of hypertension, MSKCC risk score, clinical T stage, or body mass index (Table 2). For the three patients who had organ-confined disease at presentation and underwent upfront nephrectomy, the median time from nephrectomy to metastatic disease was only 3 months, indicating rapid postoperative recurrence.

By multivariable analysis (Table 2), patients without clinical enlargement of lymph nodes at presentation had a median OS of 33.3 months, compared with 11.1 months for those with enlarged lymph nodes at presentation [$P = 0.056$; hazard ratio (HR) 3.28, 95% CI: 0.97–11.14]. Patients with an ECOG PS of 0–1 at baseline had a median OS of 16.4 months, while those with an ECOG PS of 2–3 at baseline had a median OS of 8.9 months ($P = 0.22$; HR 1.57, 95% CI: 0.77–3.19). Patients who underwent nephrectomy had a lower risk of death compared with patients who received systemic therapy only (median OS 16.4 vs 7.0 months, respectively, $P < 0.001$; HR 0.22, 95% CI: 0.09–0.51) after adjusting for ECOG PS and initial LN involvement (Fig. 1).

As shown in Table 3, in the subgroup of 38 patients who had nephrectomy, initial staging and performance status did not significantly affect survival. The median OS for Stage I–III patients was 18.9 months, whereas the median OS for Stage IV patients was 15.0 months ($P = 0.89$). In this cohort of patients who underwent nephrectomy, timing of first-line chemotherapy, stratified as pre- vs postoperative, did not affect survival. As shown in Fig. 2 and Table 4, the median OS for patients who received preoperative first-line chemotherapy was 18.1 months, compared with 15.0 months for patients who received postoperative first-line systemic therapy ($P = 0.63$). Interestingly, as shown in Fig. 3B, even in the cohort of patients with an ECOG PS of 2–3 at presentation, patients who ultimately underwent nephrectomy after receiving chemotherapy had longer survival than those who did not undergo nephrectomy (median OS 13.0 vs 5.7 months, $P = 0.045$). The difference in survival between the cohort of patients who had nephrectomy vs the cohort who did not was even larger for patients with an ECOG PS of 0–1 (18.1 months for nephrectomy patients vs 7.5 months for non-nephrectomy patients, $P < 0.001$; Fig. 3A). Additionally, as shown in Fig. 4, patients who achieved a complete radiographic response (CR), a partial response (PR) or had stable disease (SD) on first-line treatment had a median OS of 15.3 months, compared with median OS of 8.9 months for patients who had progressive disease (PD) on first-line treatment ($P = 0.065$).

Systemic Therapy and Response

All 52 patients received at least one line of systemic therapy during their treatment course. For the eight patients who received preoperative systemic therapy, the median (range) duration of first-line chemotherapy was 16.9 (15.9–38.9) weeks. One patient had a CR, four had a PR, and three had SD. Carboplatin/paclitaxel ($\pm$ bevacizumab) was the most common regimen, used in five of the eight patients. For the patients who underwent upfront nephrectomy and then received postoperative chemotherapy, 65% achieved CR/PR/SD with first-line chemotherapy, while 35% of patients had PD. In all, 14 patients did not undergo nephrectomy, and 8/14 had PD with first-line chemotherapy. Details on first-line systemic therapy are listed in Table 4.

In all, 28 (54%) of patients received targeted therapies (sunitinib, bevacizumab, bortezomib, pazopanib, sorafenib, everolimus, imatinib) during their treatment course. The median duration of single-agent targeted therapy was 8 weeks. No objective (CR or PR) responses were seen with single-agent targeted therapy. Data on targeted therapies and best responses are presented in Table 5.

The most frequently used chemotherapy regimens were carboplatin/paclitaxel ($\pm$ bevacizumab), gemcitabine/cisplatin ($\pm$ bevacizumab), gemcitabine/doxorubicin ($\pm$ bevacizumab), and dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin). A 29% objective response rate was seen in patients receiving cytotoxic chemotherapy. Further data regarding cytotoxic chemotherapy regimens used and responses achieved are presented in Table 6.

Long-term Responders

Seven patients survived for >24 months; two of them are alive without evidence of disease at >36 months from diagnosis. One of these patients had a clinical CR with preoperative chemotherapy (carboplatin/paclitaxel). At nephrectomy, the surgical specimen revealed no evidence of tumour in the resected lymph nodes and only a small focus of residual tumour in the resected kidney. The patient developed metastases to the lungs 8 weeks after nephrectomy, and was treated with multiple lines of systemic therapy (pazopanib, gemcitabine/doxorubicin, and carboplatin/paclitaxel). He had PD on pazopanib, but achieved repeat CR with carboplatin/paclitaxel. He remains off chemotherapy and free of disease 45 months from diagnosis. The other surviving patient was aged 9 years at diagnosis, and had lymph node and lung metastasis at presentation. He underwent upfront nephrectomy, followed by two lines of systemic therapy (gemcitabine/cisplatin/paclitaxel and carboplatin/paclitaxel). He is now 42 months from nephrectomy and 30 months from completion of chemotherapy, and remains with no evidence of disease to date.

Discussion

RMC is a rare and an aggressive subtype of RCC. The vast majority of patients have sickle cell trait and present with advanced disease, but even the few who present with local disease develop tumour recurrence within a few months after nephrectomy. In the present largest-reported cohort to date, the median OS of 13 months compares favourably with the historical median OS of 5 months, but the prognosis remains poor, as <20% of patients survive for >24 months.

We found that clinical lymph node involvement, lack of nephrectomy, and an ECOG PS of 2–3 at presentation, were associated with worse survival. Patients who underwent nephrectomy at some point during their course of treatment had a lower risk of death, even after adjusting for effects of lymph node involvement and ECOG PS. A limitation of the present retrospective study is that it is unclear whether the benefit of nephrectomy is due to a therapeutic effect, a confounder from more favourable tumour biology, or due to patient selection bias. While a selection bias is inherent in a retrospective study, we recommend that patients should be considered for nephrectomy when clinically appropriate. The MSKCC risk score did not appear to be an appropriate metric for selecting patients for surgery; most patients in the present study had intermediate- and high-risk disease, but over half of the poor-risk group were able to undergo nephrectomy at some point during their course of treatment. Patients who present with a high tumour burden with extensive visceral or bone metastasis or rapidly progressive metastatic disease should not undergo upfront nephrectomy, as these patients invariably will have rapid deterioration after surgery and will not be able to receive systemic therapy. However, in well-selected patients, who respond to initial chemotherapy, or who have low-volume metastasis, nephrectomy can potentially play an important role, even in the metastatic setting, with radical nephrectomy and resection of all visible retroperitoneal disease being a goal of surgery. Of note, there is no role for distant metastasectomy in this disease, in contrast to RCC. Iacovelli et al. [2] also showed a trend towards benefit of nephrectomy, although this was not statistically significant and included only small numbers of patients from each treatment centre. Our present data suggest a

therapeutic benefit from nephrectomy in selected patients whether it is performed upfront or after response to chemotherapy. However, the decision to perform nephrectomy is influenced by many patient-specific variables, so a thorough patient evaluation and a multidisciplinary deliberation are necessary before a surgical treatment plan is formulated.

In our present study, response to first-line chemotherapy was associated with a trend toward improved OS. A trend for worse outcome was noted in patients who had PD in response to first-line chemotherapy, compared with those who had SD or achieved an objective response. Based on our present results, we recommend the use of combined cytotoxic chemotherapy over single agents or targeted therapies, particularly for palliation of symptoms. Most patients in our present study received carboplatin/paclitaxel ($\pm$ bevacizumab), or gemcitabine/cisplatin ($\pm$ bevacizumab) in the first-line setting. Based on our present data, targeted agents do not appear to produce any meaningful response as single agents. Our suggested treatment algorithm for RMC is shown in Fig. 5, and focuses on the multidisciplinary management of this disease.

The next frontier in RMC research is a rigorous molecular characterisation to identify biologically relevant targets that can be exploited for the development of rational and more effective therapies. Molecular profiling of RMC has shown a signature more similar to urothelial carcinoma or TCC of the renal pelvis than to RCC [20]. Recent comprehensive genomic profiling has shown loss of *SMARCB1*, a tumour suppressor gene on chromosome 22 [21,22]. The loss of *SMARCB1* protein is becoming increasingly important in the confirmation of RMC, as shown in the recommended diagnostic algorithm in Fig. 6. In addition, balanced translocations disrupting *SMARCB1* have been reported as the hallmark of genetic alterations in RMC [23]. *SMARCB1* acts as a chromatin remodelling regulator, which is a repressor of cyclin D1 transcription; therefore, loss of *SMARCB1* leads to increased cyclin D1 transcription in RMC [24]. This has downstream effects on overexpression of EZH2 (a histone methyltransferase), providing the rationale for using EZH2 inhibitors, such as tazemetostat, as therapeutic options [23,25]. Phosphatase and tensin homologue (PTEN) loss and use of mammalian target of rapamycin (mTOR) inhibitors has also been under recent investigation, although results have been limited [26]. As we gain insights into the biology of this aggressive tumour, we hope to develop novel and more effective therapies that will lead to improved patient outcomes.

Conclusions

RMC is an aggressive disease, with limited treatment options and universally poor outcomes. In the present retrospective study, we did not observe any responses to targeted agents when used as monotherapy; however, cytotoxic chemotherapy provided palliative effects. Patients who underwent nephrectomy during the course of their disease had a longer survival than those who were treated with systemic therapy only. Timing of administration of chemotherapy (pre- vs postoperatively) did not affect survival, but a trend towards a longer survival was noted in patients who achieved an objective response or SD to first-line chemotherapy. Studies are urgently needed to identify molecular alterations that could provide the foundation for development of novel, rational, and more effective therapy for RMC.

Acknowledgments

Conflicts of interest

Dr Malouf reports grants from Pfizer, grants from Novartis, outside the submitted work; Dr Heng reports grants and consultancy fees from Pfizer, grants and consultancy fees from Novartis, outside the submitted work; Dr Guancial reports other from Genentech, outside the submitted work; Dr Fung reports personal fees from Janseen Scientific Affairs, personal fees from Dendreon, personal fees from Bayer, personal fees from Novartis, outside the submitted work; Dr Wood reports grants from Pfizer, grants from Ono Pharma, grants from Boehringer Ingelheim, personal fees from Novartis, during the conduct of the study; Dr Tannir reports grants, personal fees and non-financial support from BMS, grants, personal fees and non-financial support from Exelixis, personal fees and nonfinancial support from Nektar, grants, personal fees and non-financial support from Novartis, personal fees and non-financial support from Pfizer, personal fees and non-financial support from Argos, personal fees and non-financial support from Calithera, grants from Miranti, grants from Epizyme, outside the submitted work; Dr Shah, Dr Karam, Dr Rao, Lianchun Xiao, Dr Jonasch, Dr Vaishampayan, Dr Lowas, Dr Tamboli, Dr Sircar and Dr Martin have nothing to disclose.

Abbreviations

CR	complete response
ECOG PS	Eastern Cooperative Oncology Group performance status
HR	hazard ratio
MSKCC	Memorial Sloan-Kettering Cancer Center
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
OS	overall survival
PD	progressive disease
PR	partial response
RMC	renal medullary carcinoma
SD	stable disease

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Fig. 1.
OS: comparison of nephrectomy plus systemic therapy vs systemic therapy only ($N = 52$ patients).

Fig. 2.
OS of nephrectomy patients: comparison of preoperative systemic therapy vs upfront surgery followed by systemic therapy ($N = 38$).

Fig. 3. OS by nephrectomy and performance status. **(A)** ECOG PS 0–1; **(B)** ECOG PS 2–3.

Fig. 4.
OS by best response to first-line therapy (CR/PR/SD vs PD).

Fig. 5.
Suggested treatment algorithm. RPLND. retroperitoneal lymph node dissection.

Fig. 6.
Suggested diagnostic algorithm. IHC, immunohistochemistry.

Table 1

The patients' characteristics.

	Total	Nephrectomy	Systemic therapy only	P
Number of patients	52	38	14	
Age at diagnosis, years, median (range)	28.2 (9.4–48.1)	28.5 (9.4–48.1)	27.2 (20–47.2)	0.61
N (%)				
Gender				
Female	15 (29)	12 (32)	3 (21)	0.73
Male	37 (71)	26 (68)	11 (79)	
Race				
Black	47 (90)	34 (89)	13 (93)	1.00
Other	5 (10)	4 (11)	1 (7)	
Haemoglobinopathy				
Sickle cell trait	51 (98)	38 (100)	13 (93)	0.27
Sickle thalassaemia	1 (2)	0	1 (7)	
Tumour Side				
Right	36 (69)	29 (76)	7 (50)	0.12
Left	13 (25)	7 (19)	6 (43)	
Not available	3 (6)	2 (5)	1 (7)	
Tumour size at presentation, cm, median (range)	6.0 (3.4–11.4)	6.0 (3.9–11.4)	6.4 (3.4–9.9)	0.55
N (%)				
Clinical stage at presentation				
I	3 (6)	3 (8)	0	0.07
II	0	0	0	
III	14 (27)	13 (34)	1 (7)	
IV	35 (67)	22 (58)	13 (93)	
ECOG PS at presentation				
0	9 (17)	9 (24)	0	0.06
1	23 (44)	17 (45)	6 (43)	
2	11 (21)	8 (21)	3 (21)	
3	9 (17)	4 (10)	5 (36)	

	Total	Nephrectomy	Systemic therapy only	P
Lymph nodes at presentation	44 (85)	30 (79)	14 (100)	0.09
Metastatic sites at diagnosis				
Lymph Nodes	44 (85)			
Lungs	24 (46)			
Liver	8 (15)			
Bone	8 (15)			
Pleura	3 (6)			
Adrenal gland	2 (4)			
Psoas muscle	2 (4)			
Ovary	1 (2)			
Skin	1 (2)			
Pancreas	1 (2)			
Thyroid	1 (2)			
Brain	0 (0)			
No. of organs with metastatic disease (at any time)				
1–2	14 (27)			
>2	38 (73)			
Pathological staging	38 (nephrectomy)			
T stage				
T1	7 (19)			
T2	2 (5)			
T3	27 (71)			
T4	2 (5)			
N stage				
N0	4 (11)			
N1	24 (63)			
Nx	10 (26)			

Table 2

OS analysis.

Variable	Median OS, months (95% CI)	Univariable analysis <i>P</i>	Multivariable analysis	
			HR (95% CI)	<i>P</i>
Gender				
Female	12.3 (9.0, N/A)	0.24		
Male	13.0 (8.4, 17.9)			
Hypertension at baseline				
No	13.0 (7.8, 19.9)	0.63		
Yes	14.3 (7.0, N/A)			
Initial AJCC stage				
I	33.3 (7.2, N/A)	0.47		
III	14.3 (12.3, N/A)			
IV	11.1 (8.4, 16.4)			
Initial T stage				
1	33.3 (8.9, N/A)	0.17		
2	12.0 (10.4, N/A)			
3	13.0 (9.0, 18.1)			
4	8.4 (7.5, N/A)			
Initial LN involvement				
Yes	11.1 (8.7, 15.0)	0.01	3.3 (1.0, 11.1)	0.06
No	33.3 (19.9, N/A)			
MSKCC risk score				
0	13.7 (N/A, N/A)	0.20		
1–2	13.0 (9.0, 20.0)			
3	8.9 (7.2, 15.3)			
ECOG PS				
2–3	8.9 (4.3, 15.3)	0.008	1.6 (0.8, 3.2)	0.22
0–1	16.4 (11.0, 22.5)			
Nephrectomy				
Yes	16.4 (13.0, 22.5)	<0.001	0.22 (0.09, 0.5)	<0.001
No	7.0 (3.5, N/A)			
Response to first-line therapy				
CR/PR	12.3 (8.5, N/A)	0.11		
SD	17.9 (13.0, N/A)			
PD	8.9 (7.5, 22.5)			
Body mass index, kg/m ²				
<30	13.0 (7.8, 19.9)	0.42		
>30	18.4 (8.7, N/A)			

AJCC, American Joint Committee on Cancer.

Table 3 Subgroup analysis of nephrectomy patients ($N = 38$).

Variable	Median OS, months	OS rate at 12 months, %	<i>P</i>
Stage at presentation			
I–III	18.9	74	0.89
IV	15.0	65	
ECOG PS			
0–1	18.1	73	0.09
2–3	13.0	58	
Preoperative therapy			
Yes	18.1	71	0.63
No	15.0	68	

Table 4

First-line chemotherapy data.

Variable	Value
Pre-operative chemotherapy, <i>n</i>	
Yes	8
No	30
Duration of preoperative therapy, weeks, median (range)	16.9 (15.9–38.9)
<i>N</i> :	
Best response to preoperative chemotherapy by RECIST (<i>n</i> = 8)	
CR	1
PR	4
SD	3
PD	0
Regimens used for preoperative therapy	
Paclitaxel/carboplatin	4
Paclitaxel/carboplatin/bevacizumab	1
Paclitaxel/carboplatin/gemcitabine	1
Gemcitabine/cisplatin/bevacizumab	1
Gemcitabine/doxorubicin	1
Best response to first-line chemotherapy by RECIST in upfront nephrectomy patients	
CR	1
PR	4
SD	12
PD	9
Best response to first-line chemotherapy in non-nephrectomy patients	
CR	0
PR	4
SD	2
PD	8
Number of lines of systemic therapy throughout course	
0	0
1	20
2	9
3	11
4	12

RECIST, Response Evaluation Criteria in Solid Tumors.

Table 5

Targeted therapies used and responses achieved.

Agent	Patient no.	Line of therapy, <i>n</i>	Duration of therapy, weeks	Best response
Sunitinib	6	1	12	PD
	9	1	27	SD
	10	1	5	PD
	11	1	4	PD
	13	2	5	PD
	15	1	25	SD
	17	1	4	PD
	44	2	13	PD
	2	1 (with gemcitabine/cisplatin)	16	PR
	3	6 (with erlotinib)	20	PD
	5	1 (with gemcitabine/cisplatin)	7	SD
Bevacizumab	9	2	8	PD
	11	2 (with gemcitabine/doxorubicin)	21	PD
	12	2 (with carboplatin/paclitaxel)	10	SD
	13	1 (with erlotinib)	49	SD
	14	2 (with erlotinib)	23	SD
	17	2 (with gemcitabine/capecitabine)	10	SD
	18	2 (with carboplatin/paclitaxel)	10	SD
	19	2 (with carboplatin/paclitaxel)	17	PR
	21	2 (with carboplatin/paclitaxel)	6	SD
	24	1 (with carboplatin/paclitaxel)	18	SD
	25	1 (with gemcitabine/cisplatin)	10	PD
	26	3 (with carboplatin/paclitaxel)	43	SD
	31	2	30	SD
	36	1 (with carboplatin/paclitaxel)	26	PR
	41	2	12	SD
	46	1 (with gemcitabine/cisplatin)	6	PR
	12	5 (with everolimus)	5	PD
Sorafenib				

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Agent	Patient no.	Line of therapy, <i>n</i>	Duration of therapy, weeks	Best response
Imatinib	48	3	6	PD
	3	2 (with gemcitabine/cisplatin)	6	PD
	4	1	3	PD
	37	3 (with ipilimumab)	7	PD
Bortezomib	48	1	8	PD
	9	7	8	SD
	28	1	7	PD
	48	4	6	PD
Everolimus	9	4	11	PD
Pazopanib	20	2	9	PD

Table 6

Chemotherapy-based regimens used and responses achieved.

Agent	Patient no.	Line of treatment, <i>n</i>	Duration of therapy, weeks	Best response
Carboplatin/paclitaxel (±bevacizumab)	2	3	15	SD
	12	2	10	SD
	14	1	16	PD
	18	1	29	SD
	19	1	33	PR
	20	1	15	CR
	21	1	14	SD
	24	1	31	SD
	26	2	48	SD
	27	2	49	SD
	29	1	14	SD
	30	1	19	PR
	31	3	23	SD
	32	1	39	PR
	33	1	28	SD
	35	1	15	PR
	36	1	26	PR
	37	1	9	PD
	38	1	16	SD
	40	1	8	SD
Gemcitabine/cisplatin (±bevacizumab)	43	2	28	CR
	45	2	18	SD
	1	1	16	PR
	2	1	16	PR
	3	2	6	PD
	5	1	7	SD
	9	3	15	PD
	12	1	13	PD
	19	3	20	SD
	23	1	35	SD
Gemcitabine/doxorubicin (±paclitaxel or bevacizumab)	25	1	10	PD
	42	1	14	PR
	46	1	12	PR
	47	1	16	PD
	2	2	11	PD
	3	1	6	SD
	8	2	7	PD
	9	5	25	SD
	11	1	21	SD

Agent	Patient no.	Line of treatment, <i>n</i>	Duration of therapy, weeks	Best response
MVAC	18	2	11	SD
	19	2	24	PR
	20	3	16	SD
	30	3	10	PD
	33	2	12	PR
	52	1	27	PR
	18	4	6	SD
	26	1	7	PD
	30	2	13	PD
	31	1	14	SD
	38	2	9	PD
	41	1	20	SD
	44	1	8	SD
	45	1	24	SD
	48	2	24	PR
Gemcitabine/cisplatin/ifosfamide	49	1	12	PR
	8	1	11	SD
	16	1	2	PD
Gemcitabine/capecitabine (±bevacizumab)	26	3	17	PD
	13	3	6	SD
	14	3	10	PD
	17	2	10	SD
Gemcitabine/carboplatin/paclitaxel	21	2	8	PD
	50	1	16	SD
	51	1	22	PR
Gemcitabine/cisplatin/paclitaxel	43	1	26	CR