Clinical outcome and prognostic factors in renal medullary carcinoma: A pooled analysis from 18 years of medical literature

Roberto Iacovelli, MD; Daniela Modica, MD; Antonella Palazzo, MD; Patrizia Trenta, MD; Gabriele Piesco, MD; Enrico Cortesi, MD

Sapienza University of Rome; Department of Radiology, Oncology and Human Pathology, Oncology Unit B, Rome, Italy

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Abstract

Introduction: We describe clinical features and prognostic factors of renal medullary carcinoma (RMC) by performing a pooled analysis of all reported cases since 1995.
Methods: A systematic search was performed to identify all articles describing patients with medullary renal cancer until February 2013. Survivals were estimated using Kaplan-Meier method with 95% confidence intervals and compared across the groups using the log-rank test. The following factors were evaluated using the Cox proportional hazards model: association of extension of disease at diagnosis, response to therapy, and surgical treatment of primary tumour with overall.
Results: A total 47 articles were selected; these described 165 patients with RMC plus 1 from our centre. The median age was 21 years and 98% of cases had the sickle cell trait. The mean size of the primary tumours was 6.0 cm, with an involvement of loco-regional lymph nodes in 71% of cases. The overall survival at diagnosis was 4.0 months in metastatic patients and 17.0 months in non-metastatic patients. Patients who received platinum-paclitaxel-gemcitabine had longer control of the disease when compared to topoisomerase inhibitors or targeted therapies. The multivariate analysis confirmed that the advanced stage at diagnosis increased the risk of death of about threefold.
Conclusion: RMC is a tumour with poorer prognosis; based on these results, platinum-based chemotherapy is the preferred systemic treatment. Even if radical nephrectomy as an up-front strategy did not report a survival benefit, it may be considered to palliate local symptoms and to perform a correct diagnosis.

Introduction

Renal medullary carcinoma (RMC) is a rapidly growing tumour of the renal medulla associated almost exclusively with the sickle-cell trait. This rare tumour was first described by Davis and colleagues in 1995; they reported 34 cases collected over 22 years at the Armed Forces Institute of Pathology.[1] Over the next 5 years, only 15 more cases have been described.[2]

Patients affected by RMC are usually younger African-Americans, with a median age of 22 and affected by sickle-cell trait.[3] The diagnosis is normally performed with histological examination of the tumour, even if those could be anticipated considering the clinical characteristics of the patient and the radiological signs of a centrally located tumour with an infiltrative growth pattern, and the typical invasion of the renal sinus.[4]

Since the rarity of this tumour does not allow experimental clinical trials, the best surgical or medical approach to treat the disease remain anecdotal. Generally, these patients have a radical nephrectomy with chemotherapy in the case of metastatic disease, but the effect of surgery on general prognosis has never been investigated and the prognosis remains poor.

We aim to describe the clinical features and prognostic factors of RMC by performing a pooled analysis of all reported cases since 1995.

Methods

A systematic search using MEDLINE/PubMed was performed using the search terms: "medullary carcinoma AND kidney" published from January 1995 to February 2013. We limited the search to all English articles and articles related to humans. We also used references from selected articles to find other relevant publications related to our search. When available, data were extracted to focus on following parameters: age, sex, presence and type of symptoms, stage of disease at diagnosis, sites of metastasis, disease-free survival (DFS), overall survival (OS), progression-free survival (PFS) type of treatment and its efficacy. All data were used to create a database for final analysis.

Statistical analysis

Baseline values were expressed as median and interquartile range (IQR), with baseline defined as the date of surgery or first diagnosis whenever surgery was not performed.

DFS was defined as the length of time after surgery during which no disease was found. OS was defined as the time from surgery to death or last contact and PFS was defined as the time from the start of therapy to the progression of disease or the death for any cause. The DFS, PFS, and OS were estimated using Kaplan-Meier method with 95% confidence intervals (CI) and compared across the groups using the log-rank test.

The following factors were evaluated using the Cox proportional hazards model: association of extension of disease at diagnosis, response to therapy, and surgical treatment of primary tumour with overall. Multivariable analyses were performed using a stepwise selection approach with a type I error of 0.05 for model entry and 0.10 for elimination.

Correlations between type of therapy used and clinical benefit (defined as the sum of the partial and complete response with the stability of disease at radiological evaluation) were evaluated by the non-parametric Spearman rank test (r_s). Statistical signifance was set at $p < 0.05$.

All statistical analyses were performed using the Predictive Analytics SoftWare (PASW, v19; IBM SPSS).

Results

Initially, we retrieved 226 articles, among these 182 were immediately rejected because they were related to other subjects, reviews or preclinical experiences. Another 2 articles were found from the references of selected articles. A total of 47 articles were included in the final analysis. These articles described the clinical characteristics of 165 patients (Table 1), and 1 patient from our institution was added for a total of 166 patients (Fig. 1).

Baseline characteristics

The median age was 21 (IQR: 15–29.5), and 71% of cases were male. The African Americans and the Caucasian race were reported in 93% and 7% of the valuable cases, respectively; whereas the sickle-cell trait was found in 97.7% of patients (Table 2).

The main symptoms at diagnosis, found in 67% of cases, were hematuria and pain. Weight loss was found in 23% of cases, whereas respiratory symptoms related to pleural effusion or bulky disease, nausea and/or vomiting and the detection of a renal mass were present in less than 10% of patients.

The mean size of the primary tumours at diagnosis was 6.0 cm (IQR: 4.7–8.0), and the involvement of loco-regional lymph nodes was reported in 70.8% of cases. The diagnosis was performed in the advanced stage in 80.5% of cases and half of these had a tumour greater than 6 cm. Of the total cases, 71.3% and 31.3% of patients had almost one or two sites of metastasis at the diagnosis, respectively. The most frequent sites were subdiaphragmatic nodes, lungs, liver, and local relapse or contralateral kidney (Table 3).

Treatments and survivals

The median OS was 5.0 months (95% CI, 2.4–7.6); this was longer in non-metastatic patients compared to patients with advanced disease at diagnosis (17.0 vs. 4.0 months; $p = 0.001$) (Fig. 2, part A). A total of 83.5% of patients had nephrectomy or tumour embolization (1 case), and survival was better in those patients compared to who did not have the nephrectomy or tumour embolization (6.0 vs 3.0 months; $p = 0.037$) (Fig. 2, part B). Among the 20 patients who did not received nephrectomy, the diagnosis was performed by biopsy of the renal mass in 7 cases, by biopsy of supraclavicular node in 4 cases, by autopsy in 3 cases, by urinary cytology in 1 case; data were not available in the remaining cases. In non-metastatic patients after treatment of the primary tumour, the median DFS was 8.0 months (95% CI, 2.7–13.2). A non-significant benefit for radical nephrectomy was found in metastatic patients (5.0 vs. 2.0 months; $p = 0.067$).

Information about medical treatments was available for 55 cases and among these 48 received first-line chemotherapy and 6% a treatment with target agents or interferon (IFN). In patients who received chemotherapy, platinum-based treatment was administered in 59% of cases (Table 4).

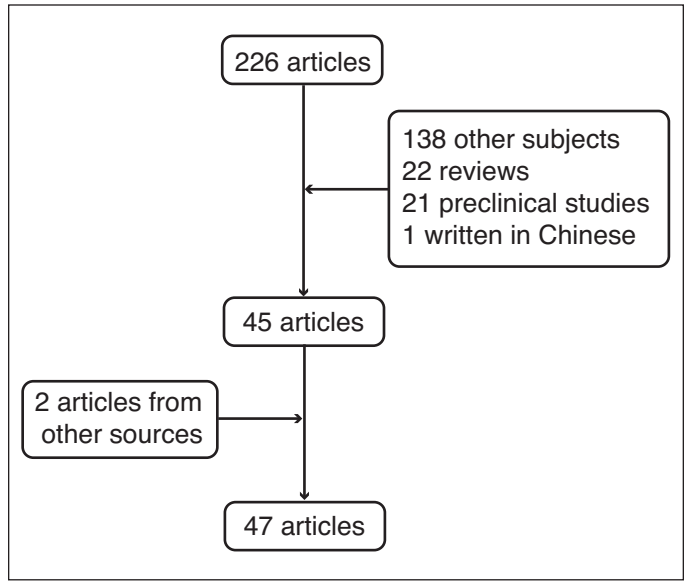

Fig. 1. Flow-chart of study selection.

Table 1. Studies included in the final analysis

Authors	PubMed ID	Cases
Adsay N.V. et al.	9500230	1
Assad L. et al.	15593260	3
Avery R.A. et al.	8646708	6
Bell M.D. et al.	16514612	1
Coogan C.L. et al.	9609653	3
Davis C.J. et al.	7528470	33
Diao B. et al.	20656278	1
Dimashkieh H. et al.	12653601	2
Ellen A. ronnen et al.	16549825	1
Ellis C.L. et al.	19526572	2
Friedrichs P. et al.	9120938	1
Gangireddy V.G. et al.	22409864	2
Gatalica Z. et al.	21733559	3
Hakimi A.A. et al.	18068443	9
Herring J.C. et al.	9146631	1
Jeanette D. Hoenig et al.	12013017	1
Johnson R.P. et al.	21048487	1
Kalyanpur A. et al.	9308460	1
Khabir A. et al.	16309940	1
Khan A. et al.	10930759	1
Larson D.M. et al.	9557262	1
leitao V.A. et al.	16549825	1
Mathur S.C. et al.	11035600	1
Milhoua P.M. et al.	18631900	1
Muhammad A.B. et al.	2569460	1
Nava V.E. et al.	21915032	1
Neville A. et al.	17406914	1
Noguera-Irizarry W.G. et al.	14528077	1
Pickhardt P.J. et al.	11222193	1
Pirich L.M. et al.	10029817	1
Qi J. et al.	11575652	1
Rao P. et al.	22301499	14
Rathmell W.K. et al.	18649931	3
Sathyamoorthy K. et al.	16691241	1
Selby D.M. et al.	10737506	1
Sherburne R. et al.	9474131	2
Simpson L. et al.	15879768	3
Stahlschmidt J. et al.	10573578	1
Strouse J. et al.	15602719	2
Swartz M.A. et al.	12475675	40
Vargas-Gonzalez R. et al.	14530815	1
Walsh A. et al.	20979179	1
Warren K.E. et al.	9925868	1
Watanabe I. et al.	17643096	7
Wesche W.A. et al.	9566287	1
Yang X.J. et al.	14983493	2
Total no. cases		165

In metastatic patients at diagnosis, the median OS was 10.0 months in patients who received any platinum-based chemotherapy for advanced disease compared to 5.0 months in patients who did not, but difference was not significant ($p = 0.098$). A positive correlation was found between the use of platinum-based regimens, and the clinical benefit at first-line treatment ($r_s = 0.49$, $p = 0.005$); moreover, patients who achieved clinical benefit had better OS compared to those who did not (12.0 vs. 4.0 months; $p = 0.010$).

Patients who received the cisplatin, paclitaxel and gemcitabine regimen (CPG) experienced longer PFS (8.0 vs. 1.0; $p = 0.028$) and longer OS (12.0 vs. 7.0: $p = 0.031$) compared to patients who received topoisomerase inhibitors. Better survivals were reported in patients treated with CPG compared to the MVAC regimen: 8.0 versus 1.0 months for PFS ($p = 0.064$) and 12.0 versus 4.0 months for OS ($p = 0.058$), respectively – this is clinically, although not statistically, significant.

Table 2. Clinical characteristics of the entire cohort and symptoms at diagnosis

No. patients	166
Male sex	70%
Median age (IQR)	21 years (range: 15–30)
Patients over 20 years old	53.3%
Race	
Afro-American	93%
Caucasian	7%
Sickle cell trait	97.7%
Type of symptoms	
Hematuria	67.6%
Pain	67.6%
Weight loss	23.5%
Mass	9.0%
Respiratory distress	8.8%
Nausea vomiting	6.9%

IQR: interquartile range.

Prognostic factors

We performed a univariate and multivariate analysis to test if baseline characteristics, such as age ≥20, sex, stage at diagnosis, nephrectomy, primary tumour extension, and metastatic stage at diagnosis, affected survival. Two factors were dependent prognostic factors at univariate analysis: nephrectomy and metastatic stage at diagnosis. The multivariate analysis only confirmed the independent prognostic role of metastatic stage at diagnosis (hazard ratio 2.71, 95% CI 1.42–5.16; $p = 0.003$) (Table 5).

Discussion

RMC is a rare tumour characterized by little data about its pathogenesis. Pathologically, the renal medulla is characterized by anoxia, hyperosmolarity and low pH that promote hemoglobin S polymerization and red blood cell sickling.

Table 3. Characteristics of primary tumour and extension of disease at diagnosis

Mean size	6.0 cm (range: 4.7–8.0)
IV stage at diagnosis	80.5%
N° of metastatic sites	
>1	71.3%
>2	31.3%
Metastatic sites	
Sub-diaphragmatic nodes	70.8%
Lung	47.8%
Liver	26.8%
Kidney/surgical site	13.3%
Adrenal gland	13.3%
Upper-diaphragmatic nodes	12.4%
Bone	12.4%
Peritoneum	7.1%
Pleural	5.3%

At the same time, the red blood cell sickling could cause obstruction of blood vessels and tissue hypoxia resulting in renal infarction and nephrotic syndrome, and subsequently gross hematuria, papillary necrosis, inability to concentrate the urine and pyelonephritis.[5,6] All these conditions worsened the hypoxic state considering the trigger for neoplastic transformation.[7]

This hypoxic phase was demonstrated by the high level of immunohistochemical expression of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF) in RMC cells, suggesting a possible common pathogenesis with classical clear-cell renal carcinoma (RCC).[7] Despite this evidence, the gene expression profile has evidenced a specific pattern of gene's amplification or deletion among RMC and clear-cell or papillary RCC that indicated a distinctive biology and probably the need for different modalities of treatment.[8]

Stahlschmidt and colleagues reported several numerical and structural chromosome changes, including isochromosomes for 1q, 8q and 17q, translocation between chromosomes 10 and 16, and between chromosomes 9 and 22, and rearrangement of the chromosomes 22 at q11. Moreover, the fluorescence in situ hybridization (FISH) analysis reported the translocation 9:22 contained a bcr/abl rearrangement commonly seen in chronic myeloid leukemia.[9] On the contrary, other authors did not report any genetic change in 9 out of 10 cases and only loss of chromosome 22 was described in 1 case.[7,8]

Radiologically, the RMC can be characterized by the extension in the renal sinus that can cause distortion of the renal collecting system on intravenous urography. The contrast-enhanced computed tomography and magnetic resonance imaging show an infiltrative growth pattern from the renal medulla toward the renal cortex laterally, and the renal pelvis and sinus medially. The tumour may cause overall expansion of the kidney, while maintaining the reniform contour. Its medullary origin can be difficult to appreciate in cases of large masses; when the tumour is centrally located, it is often associated with caliectasis without pelviectasis. After contrast administration, some heterogeneous areas can be seen due to necrotic and hemorrhagic areas. These can appear as signal void on T2-weighted images with longer

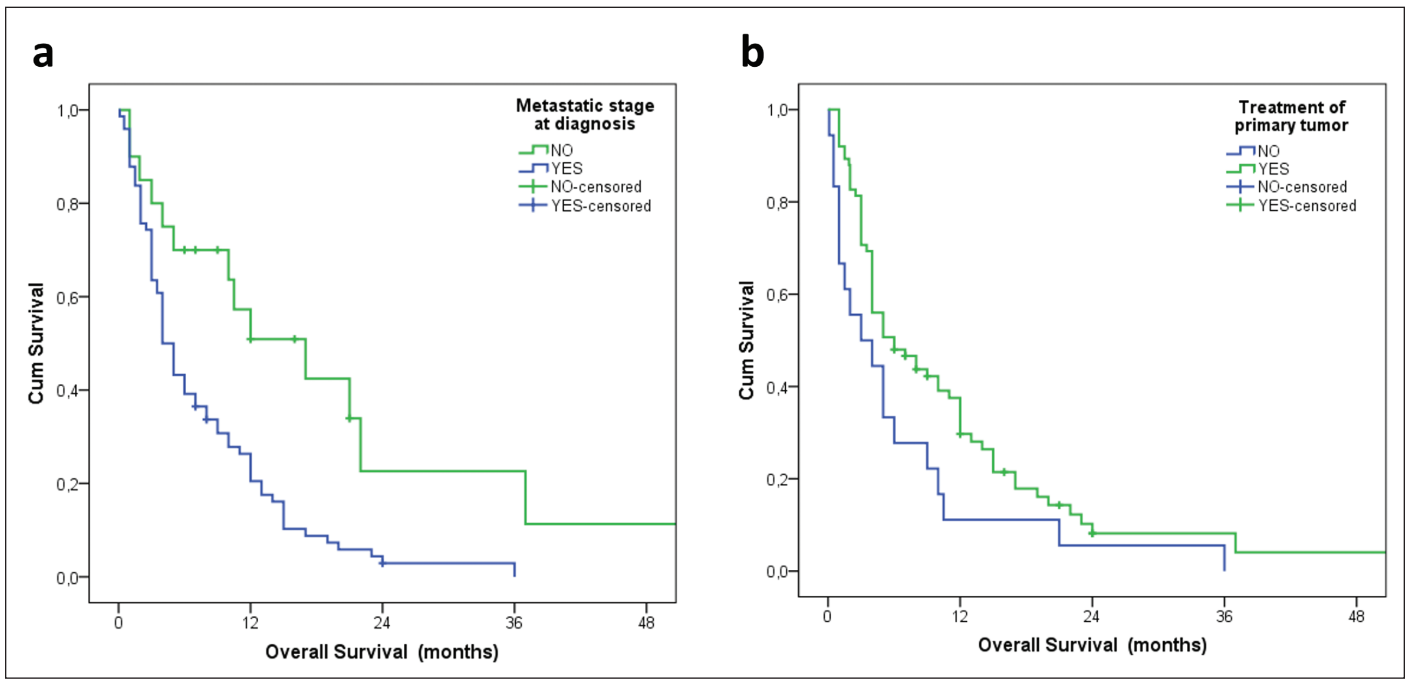

Fig. 2. Impact of metastatic stage at diagnosis on overall survival (A) and impact of radical nephrectomy on overall survival (B).

Table 4. Surgical and medical treatments received by analyzed patients

Treatments	Patients, %
Nephrectomy	83.5%
Medical treatment	87.7%
First line	56 patients
Chemotherapy	89.3%
Target agents	8.9%
Immune treatments	1.8%
Type of chemotherapy	
CPG	10.9%
MVAC	28.3%
Response	27 patients
CR+PR+SD	26.9%
PD	73.1%
Second line	15 patients
Chemotherapy	100%

CPG: cisplatin, paclitaxel and gemcitabine regimen; methotrexate, vinblastine, doxorubicin, and cisplatin; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

echo times due to the susceptibility effect caused by products of hemorrhage.[10,11]

The clinical role of angiogenesis as a possible target was recently discarded by a retrospective review about 30 patients with RMC treated at 4 institutions in the United States between 2000 and 2010.[12] Six of these patients received the anti-angiogenic agent alone as up-front therapy and none achieved a response; whereas, only 1 patient achieved a response with erlotinib and bevacizumab when used as second-line. On the other hand, a higher rate of responses in first- and second-line was obtained in patients treated with chemotherapy.

Collecting all data reported in medical literature in the last 18 years, we were able to report the largest dataset about this disease and analyze clinical and prognostic features. We were able to find that most patients were symptomatic at diagnosis and we confirmed their poorer survival, at a median OS of 4 months in metastatic patients and less than 17 months in non-metastatic ones.

Moreover chemotherapy induced a positive response in patients and patients treated with platinum-based combinations had an increase in PFS. These results should be considered in light of this rare disease and the consequent lack of data about its management in clinical practice.

In the attempt to increase the activity of chemotherapy, several authors have investigated the role of topoisomerase-II-α (TopoII-α) in RMC. TopoII-α is an enzyme involved in cell proliferation, DNA maintenance and repair; it is targeted by some agents, such as anthracyclines and etoposide.[8,13] Albadine and colleagues found that TopoII-α was overexpressed in 85% of RMC cases; moreover, these tumours were characterized by a high rate of proliferation and short survival.[13] Interestingly, no TopoII-α amplification was detected by FISH in the same patients suggesting that potential mechanisms, other than gene amplification, are responsible for TopoII-α overexpression in RMC.[13] This evidence limits the possibility to predict tumour cell's sensibility to specific inhibitors.

In our review group, 52% of treated patients received first-line chemotherapy with a least one TopoII inhibitor as anthracyclines or etoposide with or without cisplatin. No survival benefit was found compared to triplets or other chemotherapy regimens.

We were unable to report on the role of other prognostic factors, with the exclusion of the advanced stage at diagnosis. The data on the effect of nephrectomy on survival is marginal.

Another limitation of this paper is its retrospective nature. Data were extrapolate from published articles and not from patient charts. Patients were treated at different hospitals and different times for radiological and clinical evaluations. Finally, we did not achieve a high level of evidence due to the heterogeneity of the data.

Conclusion

We describe the clinical and prognostic cahrateristics of the largest group of patients affected by RMC. Despite our results, more efforts are needed to better understand the biology of this disease and to improve treatment strategies.

Competing interests: The authors declare no competing financial or personal interests.

Table 5. Univariate Cox analysis for overall survival in metastatic patients

Factors	Univariate Cox regression analysis		Multivariate Cox regression analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age ≥20 years old	0.82 (0.54 – 1.24)	0.37		
Sex (M/F)	0.96 (0.60 – 1.56)	0.88		
Primary tumour <6 cm (Y/N)	0.55 (0.20 – 1.06)	0.07		
Nephrectomy (Y/N)	0.59 (0.35 – 0.99)	0.048	0.60 (0.35 – 1.02)	0.061
Metastatic at diagnosis (Y/N)	2.57 (1.38 – 4.77)	0.003	2.71 (1.42 – 5.16)	0.003

HR: hazard ratio; CI: confidence interval; Y: yes; N: no; M: male; F: female.

This paper has been peer-reviewed.

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Correspondence: Dr. Roberto Iacovelli, Sapienza University of Rome; Department of Radiology, Oncology and Human Pathology, Oncology Unit B. Viale Regina Elena 324, 00161 Rome, Italy; roberto.iacovelli@alice.it