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Clinical outcome in patients receiving systemic therapy for metastatic sarcomatoid renal cell carcinoma: A retrospective analysis

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Abstract

OBJECTIVES—Sarcomatoid metastatic renal cell carcinoma (mRCC) represents an aggressive subset of disease, and a definitive therapeutic strategy is lacking. We seek to define outcomes associated with systemic therapy (including immunotherapy, cytotoxic therapy, and targeted agents) for sarcomatoid mRCC, with attention to novel prognostic schema.

MATERIALS AND METHODS—From an institutional database including 270 patients with mRCC, we identified 34 patients with documented sarcomatoid features. Within this cohort, we assessed 21 patients who received systemic therapy. Survival was assessed in the overall cohort and in subgroups divided by clinicopathologic characteristics, including the extent of sarcomatoid features, Memorial Sloan-Kettering Cancer Center (MSKCC) risk criteria, Heng criteria, and the nature of systemic therapy rendered.

RESULTS—Of the 21 patients assessed, 2 patients received chemotherapy, 7 patients received immunotherapy, and 12 patients received targeted agents as their first line treatment. Median overall survival (OS) in the overall cohort was 18.0 months (95%CI 6.9–22.0). By MSKCC criteria, patients with poor-risk disease had a median OS of 4.7 months, as compared to 20.1 months for patients with intermediate-risk disease (hazard ratio, HR, 0.02, 95%CI 0.003–0.15; P=0.0001). A similar difference in median OS was seen poor- and intermediate-risk groups when stratifying by Heng criteria (HR 0.17, 95%CI 0.001–0.12). There was no significant difference in survival in patients with sarcomatoid predominant disease *vs* non-predominant disease (HR 0.62,

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95%CI 0.23–1.65; P=0.34), nor was there a difference amongst patients who received targeted therapies *vs* non-targeted therapies (HR 1.0, 95%CI 0.61–1.40; P=0.36).

CONCLUSIONS—As compared to previous series and prospective trials assessing patients with sarcomatoid mRCC, the observed survival was prolonged. Although both Heng and MSKCC risk scores may be useful in determining prognosis, further studies are needed to identify relevant biomarkers and define the optimal therapeutic strategy for this disease.

Keywords

Survival; response; chemotherapy; targeted therapy; sorafenib; sunitinib; sarcomatoid renal cell carcinoma

Introduction

The treatment of metastatic renal cell carcinoma (mRCC) has evolved markedly over the past decade with the introduction of targeted therapies. Over the past five years, a total of 6 agents have been approved.[1] Broadly, these agents can be divided into two mechanistic categories – (1) inhibitors of vascular endothelial growth factor receptor (VEGFR) signaling, and (2) inhibitors of the mammalian target of rapamycin (mTOR). Agents in the former category include ligand inhibitors (bevacizumab) and small molecule VEGFR tyrosine kinase inhibitors (VEGF-TKIs; sunitinib, sorafenib and pazopanib).[2–5] At present, two mTOR inhibitors, temsirolimus and everolimus, are approved.[6–7]

The preponderance of phase III studies leading to the approval of the agents were comprised of patients with predominantly clear cell histology. However, one histologic subtype that remains a therapeutic conundrum is the sarcomatoid variant of RCC. Sarcomatoid features may co-exist with any histologic subtype of RCC, and the presence of these features portends a poorer prognosis. As delineated in Table 1, a retrospective series by Kuroda *et al* including 30 patients treated with a wide variety of systemic strategies (i.e., cytotoxic therapy, immunotherapy and targeted agents) have reported a median overall survival (OS) of 3.6 months. A series from the Cleveland Clinic focusing more exclusively on patients receiving targeted therapies (specifically, VEGF-directed agents) did report a more favorable OS (11.8 months). Prospective studies assessing systemic strategies for sarcomatoid mRCC have produced sobering results; to date, these studies have only assessed cytotoxic regimens. For instance, Eastern Cooperative Oncology Group (ECOG) trial 8802 examined the combination of doxorubicin with gemcitabine in 39 patients with locally advanced or metastatic RCC with sarcomatoid features.[8] Six patients (16%) experienced responses, and 10 further patients (26%) had stable disease. The median OS in this study was 8.8 months. In a separate study, Escudier *et al* assessing the combination of doxorubicin with ifosfamide in a similar population – no objective responses were observed, and median OS was 3.9 months.[9]

Given the limited prognosis associated with cytotoxic therapy for sarcomatoid mRCC, prospective studies are greatly needed to address the role of the targeted therapies in this disease. Only two such studies are currently ongoing; both examine combinations of cytotoxic therapy with VEGF-directed agents (see *Discussion*).[10–11] Until further prospective data is available, the clinician will have to rely on retrospective data and anecdotal reports to guide use of immune-directed therapies, cytotoxic therapy and targeted agents in patients with sarcomatoid RCC. To contribute to this sparse body of literature, we report an institutional experience including patients treated for sarcomatoid mRCC over the past decade.

Methods

Patients

Patients with a primary diagnosis of renal cell carcinoma diagnosed from January 2000 onwards were identified from an institutional database. Of 562 patients, a total of 270 patients were noted to have stage IV disease. Within this subset, a total of 34 patients were noted to have sarcomatoid features based on pathologic analysis performed at the institution. Of the 34 patients, 13 received no systemic therapy for metastatic disease. Clinicopathologic information was collected on the aforementioned patients through an existing institutional review board-approved protocol (IRB 11079). Notably, this is a retrospective chart review, so the frequency of laboratory analyses and tumor assessments were at the discretion of the treating clinician.

Pathologic Analysis

Per institutional requirements, pathologic tissue is reassessed to confirm diagnoses prior the initiation of therapy at City of Hope. Thus, a detailed pathology report is available for all patients included in the current protocol. However, tissue obtained from outside institutions is returned to the institution of origin (per internal policy), so archival specimens were not consistently available for analysis. The degree of sarcomatoid features was characterized as either “predominant” or “non-predominant”, on the basis of pathology reports indicating ≥20% or <20% involvement by sarcomatoid elements (as per Golshayan *et al*).[12]

Statistical Analysis

Descriptive statistics were used to characterize patients in this series. Memorial Sloan-Kettering Cancer Center (MSKCC) criteria were applied to assign good-, intermediate- and poor-risk status.[13] Separately, Heng criteria were applied to assign similar risk groups.[14] Overall survival (OS) was characterized as the time elapsed between diagnosis with metastatic disease and time of death. OS was summarized using the Kaplan-Meier method. Survival in sarcomatoid predominant and non-predominant subsets were compared in the overall cohort and in cohorts divided by treatment strategy using the student’s T-test. All data analyses were performed using SAS version 9.1.

Results

Patient Characteristics

Of 21 patients identified who received systemic for sarcomatoid mRCC, 2 patients received chemotherapy, 7 received immunotherapy, and 12 patients received targeted agents as their first line of therapy. As noted in Table 2, the median age at diagnosis was 54 (range, 35–80), and the cohort included 17 males and 4 females.

Both patients treated with cytotoxic therapy received adriamycin and gemcitabine. Of 7 patients receiving immunotherapy, 5 patients received high-dose IL-2, while 2 patients received IL-2 in combination with interferon-α. Amongst 12 patients receiving first-line targeted therapy, 8 patients received sunitinib, while 4 patients received sorafenib. No patients receiving chemotherapy as first-line treatment subsequently received targeted therapy. However, one patient who was treated initially with high-dose IL-2 received subsequent targeted agents, and another received cytotoxic chemotherapy. Two 2 patients who received first-line therapy with targeted agents did receive cytotoxic therapy thereafter. No patients who initially received targeted agents received subsequent immunotherapy.

Only one patient in the cohort was characterized as good risk by MSKCC criteria. Of the remaining patients, 14 patients were noted to be intermediate risk, while 6 patients were

poor risk. Characterization by the more recent Heng criteria led to a similar distribution by risk group, with 1, 16, and 4 patients characterized as having good, intermediate, and poor risk, respectively. Thirteen patients had sarcomatoid predominant disease, while 8 patients had non-predominant disease.

Clinical Outcome

Median OS in the overall cohort was 18.0 months (95%CI 6.9–22.0; Figure 1). As shown in Figure 2A, median OS was 8.2 months in patients with predominant sarcomatoid features as compared to 20.4 months in patients with non-predominant sarcomatoid features, although this difference was not statistically significant (hazard ratio, HR 0.62, 95%CI 0.23–1.65; P=0.34). By MSKCC criteria, patients with poor-risk disease had a median OS of 4.7 months, as compared to 20.1 months for patients with intermediate-risk disease (HR 0.02, 95%CI 0.003–0.15; P=0.0001) (Figure 2B). A similar difference in survival was seen in stratifying patients by Heng criteria, with a median OS improved in intermediate versus poor risk patients (HR 0.17, 95%CI 0.001–0.12) (Figure 2C). By both MSKCC and Heng criteria, only one patient was noted to have good risk disease – thus, no comparative statistics are offered for this risk group. With respect to treatment, survival 18.3 months in patients receiving first-line targeted agents and 18.4 months in patients receiving first-line non-targeted therapies (HR 1.0, 95%CI 0.61–1.40; P=0.36) (Figure 2D). Non-targeted therapies included IL-2 and cytotoxic chemotherapy.

Discussion

The optimal systemic therapy for patients with sarcomatoid mRCC has yet to be defined. Published data pertaining to sarcomatoid mRCC therapy is limited to phase II studies evaluating cytotoxic regimens. Furthermore, data to support the use of targeted therapies in this domain is entirely retrospective. As such, the current dataset adds to a limited body of literature, and provides insights into the use of both targeted and non-targeted strategies for this disease. The dataset also suggests the potential utility of both MSKCC and the more recent Heng criteria in prognosticating within this specific population. To our knowledge, this is the first report suggesting the potential utility of Heng criteria in defining prognosis amongst patients with sarcomatoid mRCC. Notably, these criteria were derived through evaluation of patients who were received VEGF-directed therapies as their first line of treatment, as did a substantial proportion of the current cohort.

The results presented herein are unique in several respects. For instance, the median OS of the entire cohort (18.0 months) far exceeds the reported median OS in other reports. Golshayan *et al* reported a median OS of 11.8 months in a cohort of 43 patients treated with targeted agents at the Cleveland Clinic. A key difference that may account for this is the proportion of patients with poor risk disease in both cohorts. For instance, in our study, 23% of patients were characterized as having poor risk disease, as compared to 51% in the report by Golshayan *et al*. Interestingly, when applying a cut-off of 20% sarcomatoid features, our cohort did include a larger proportion of patients with sarcomatoid predominant disease (62% *vs* 38%). On this basis, the difference in observed outcome is challenging to reconcile.

Haas *et al* performed a prospective evaluation of doxorubicin in combination with gemcitabine in a cohort of 39 patients with sarcomatoid mRCC.[8] Median OS in this cohort was 8.8 months. Although cumulative data for each Motzer score criterion (i.e., LDH, Karnofsky performance status, etc.) are provided, survival based on good-, intermediate-, or poor-risk classification is not reported. Furthermore, a differing threshold was used for classification of sarcomatoid predominant disease (75%). Using this higher cut-off, the HR for survival in patients with non-sarcomatoid disease was 0.65 (95%CI 0.24–1.72; P=0.38) in our cohort, comparable to the HR derived from using the cutoff of 20% proposed by

Golshayan *et al* (HR 0.62, 95%CI 0.23–1.65; P=0.34). The cutoff proposed by Golshayan *et al* was derived through recursive partitioning, whereas the cutoff of 75% used by Haas *et al* was initially used as an enrollment criterion. In the current analysis, neither cutoff was a significant predictor of survival. The prognostic and predictive value of these thresholds remains to be seen.

Scant data are available to assess the role of immunotherapy in sarcomatoid RCC. A retrospective report from the University of California, Los Angeles, group assessed a cohort of 31 patients with sarcomatoid RCC who had received nephrectomy.[15] Of this cohort, 28 patients (84%) had metastatic disease, and 9 patients received high-dose interleukin-2 (IL-2). Improved survival was seen in those patients receiving HD IL-2 as compared to those who did not (P=0.025). However, major inferences from this series are challenged by the small sample size. In our series, no major differences were seen in survival amongst cohorts treated with targeted strategies and immunotherapy. It is challenging to imagine prospective studies directly comparing these approaches, and thus, the decision between immunotherapy and targeted therapies in this setting is likely to remain a therapeutic dilemma.

Ultimately, the treatment of sarcomatoid mRCC may be refined through a better understanding of the biology of the disease. In an assessment of 12 RCC patient-derived cell lines, Jakobsen *et al* identified a lack of both β_2-microglobulin expression and major histocompatibility complex (MHC) class I expression in a cell line derived from a patient with sarcomatoid disease.[16] Notably, β_2-microglobulin allows for appropriate folding of MHC class I complex on the cell surface – the lack of this complex precludes antigen presentation and allows for immune invasion. In a separate effort, Kuriowa *et al* performed a detailed immunohistochemical analysis of 12 specimens derived from patients with sarcomatoid RCC.[17] The carcinomatous component of these specimens were compared to the sarcomatoid component. Interestingly, E-cadherin expression in the sarcomatoid component was consistently lower in the sarcomatoid of specimens as compared to the non-sarcomatoid component. Since E-cadherin plays an integral role in intracellular adhesion, decreased expression may explain the greater malignant potential of sarcomatoid disease. A more recent report assessing 21 specimens derived from patients with sarcomatoid mRCC with clear cell features similarly suggested low E-cadherin expression in the sarcomatoid component as compared to the clear cell component (P=0.0004), but no change in N-cadherin (P=0.46).[18] Further, Snail and SPARC expression were also increased in the sarcomatoid component (P=0.002 and P<0.0001, respectively). The combination of these features suggests that sarcomatoid disease may be a manifestation of the epithelial to mesenchymal transition (EMT). In the current study, existing pathology reports were used to determine the presence and extent of sarcomatoid features. We plan to obtain the associated archival tissue and perform detailed analysis of EMT markers to further explore the aforementioned findings.

Limitations of this study include retrospective data collection, which limit the ability to interpret therapeutic response. Patients in the study were not evaluated for response at consistent intervals, and retrospective characterization of response is subject to interpreter bias. It is unclear how, in the report by Golshayan *et al*, such bias was avoided – though a subset of patients in this study had responses assessments as a part of inclusion in prospective trials many of the patients included had therapeutic responses characterized retrospectively. The current study is also challenged by the limited sample size. As such, it is challenging to make substantial inferences from the similar survival observed in the comparisons made herein – for instance, larger sample sizes are most certainly needed to establish whether targeted or non-targeted therapies represent a superior therapeutic approach. Similarly, larger cohorts are needed to determine the implications of prognostic

schema that are applicable to generalized populations of patients with mRCC (i.e., the MSKCC and Heng criteria). Another caveat of the current study is the inability to assess therapeutic tolerance and quality of life (QOL). Given its retrospective nature, acquisition of such variables would be inherently biased. Future prospective studies would be wise to capture such variables using standard indices for both toxicity and QOL.

Despite its limitations, the current study does contribute to the limited body of literature for sarcomatoid mRCC. The preponderance of published data in this domain are anecdotal reports suggesting the efficacy of a wide array of treatment options. Efforts are greatly needed to amalgamate the existing data to support a specific treatment approach. As noted previously, ongoing phase II studies may support a strategy of combining targeted agents and cytotoxic therapies. However, it is unlikely that phase III studies will be performed in this relatively infrequent disease subtype, and thus, clinicians and investigators will be perpetually challenged to compare any and all relevant datasets.

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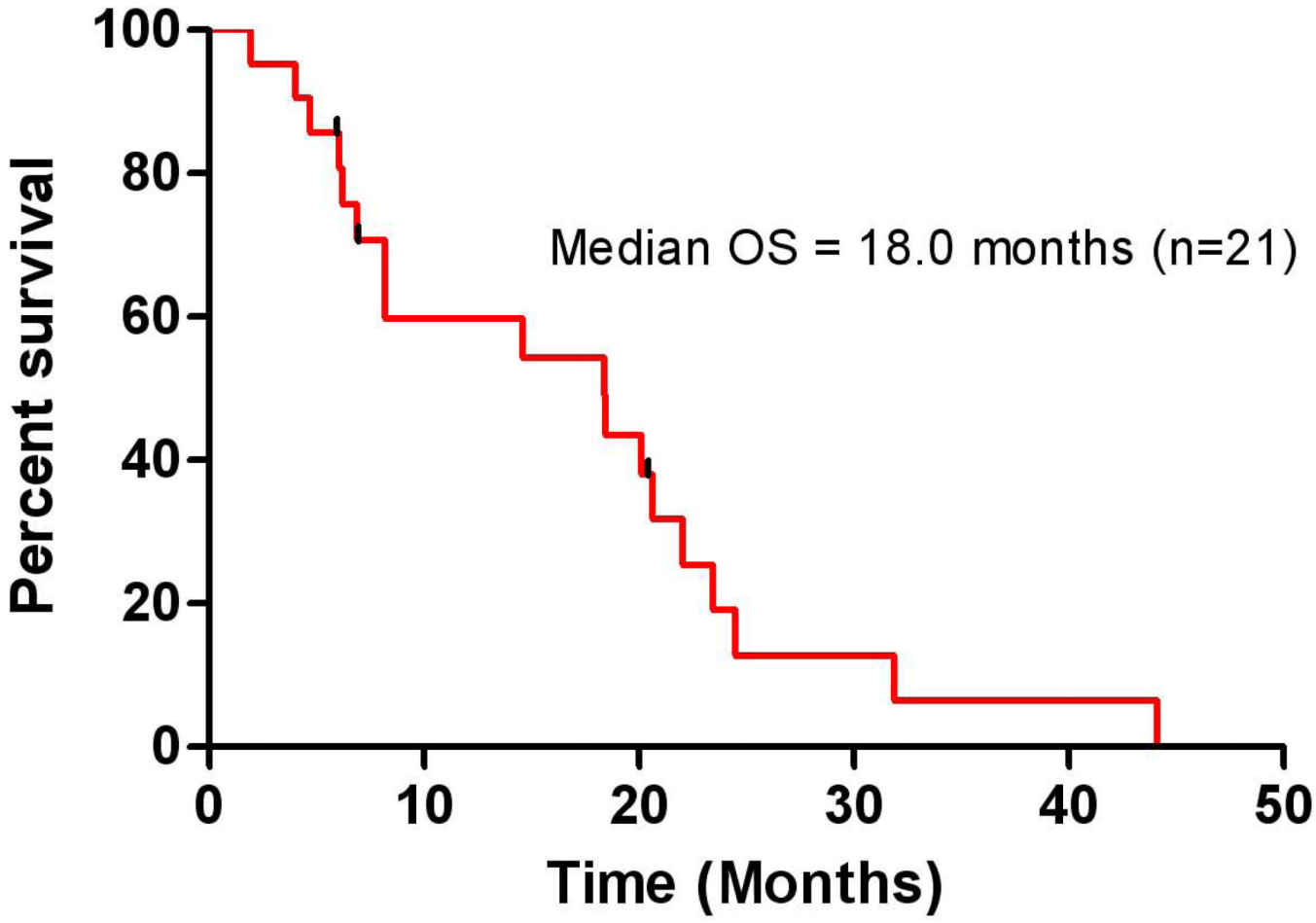
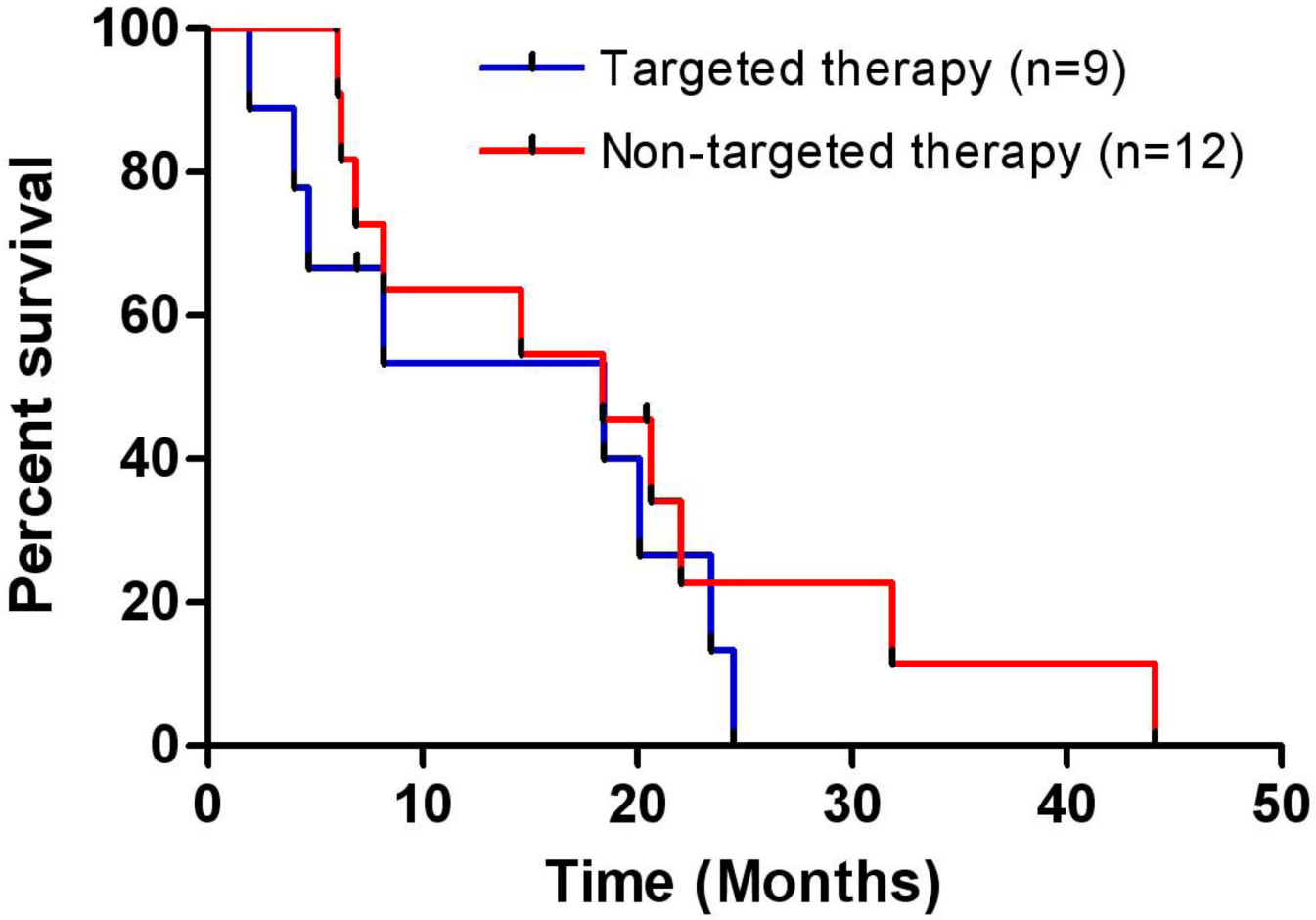
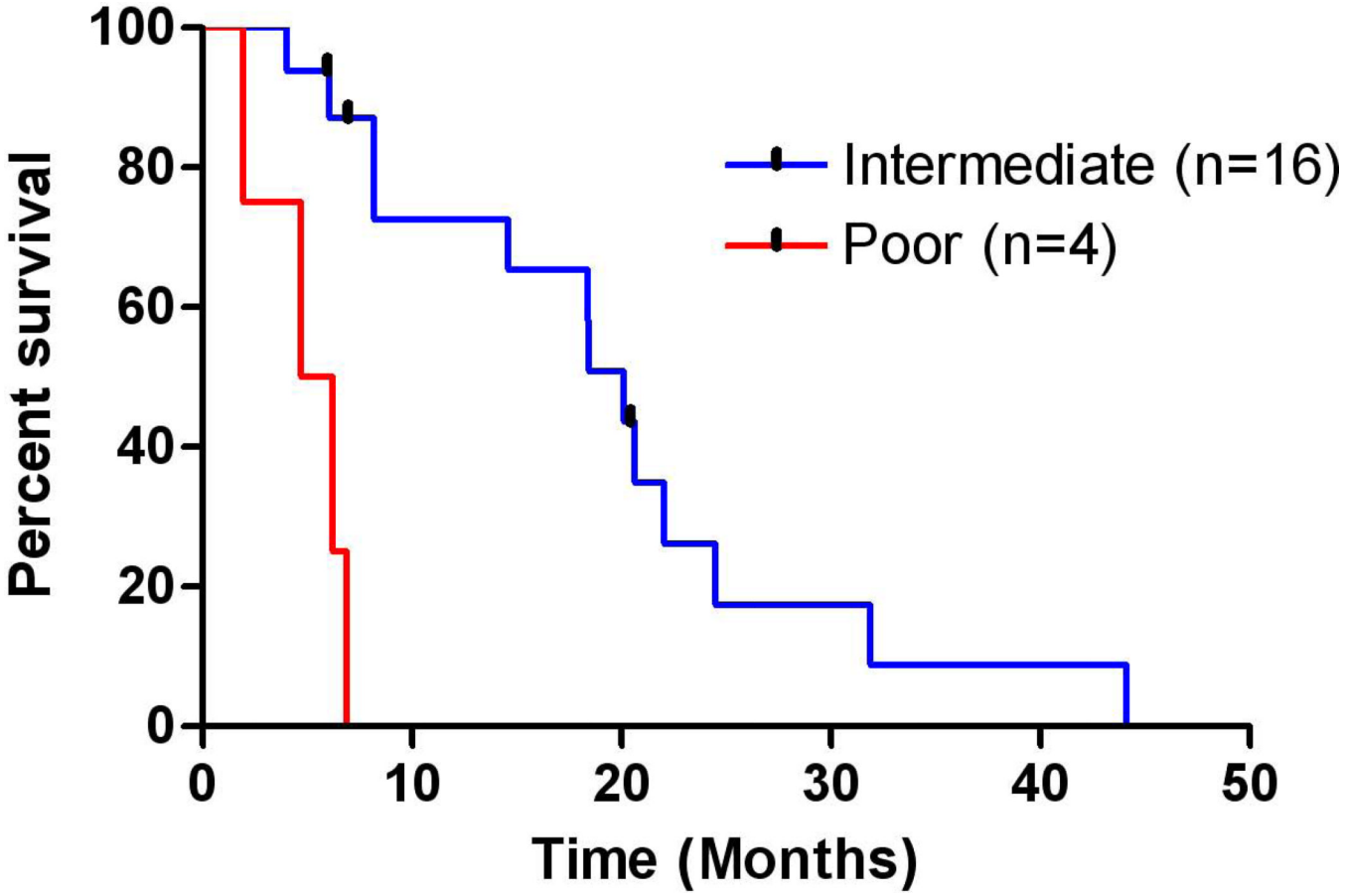
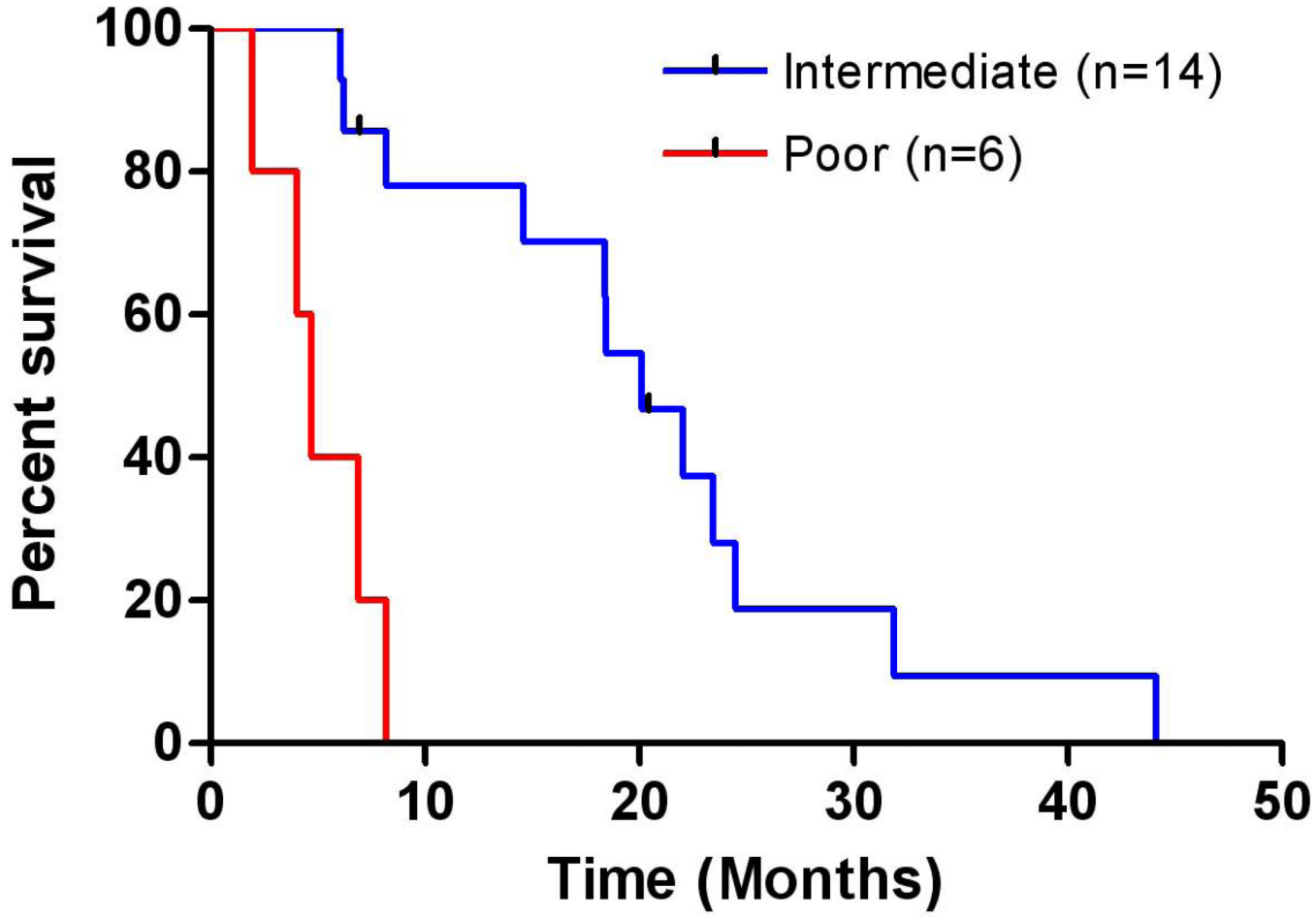


Figure 1.
Survival in patients with sarcomatoid mRCC receiving systemic therapy.







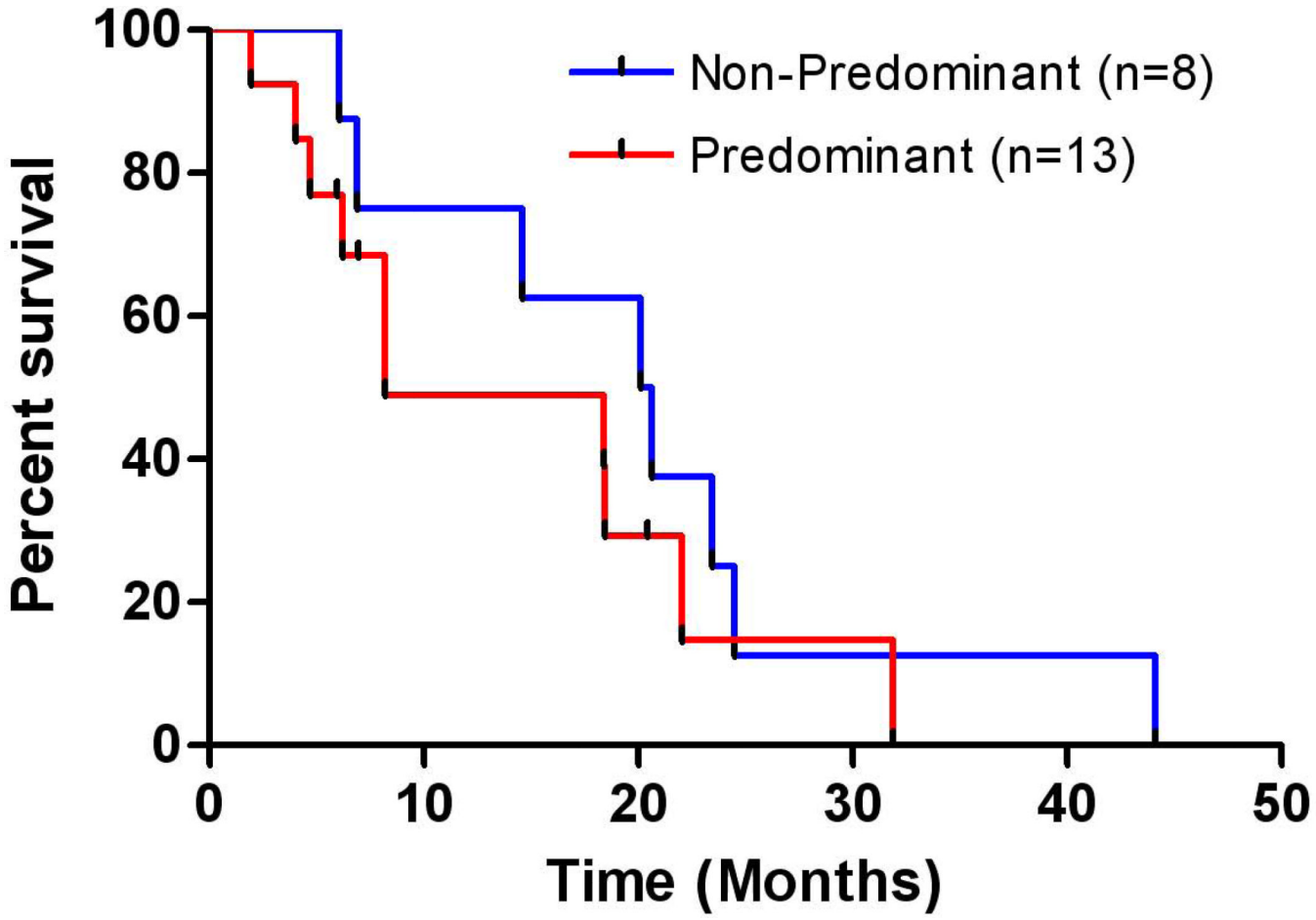


Figure 2.
Survival in patients with sarcomatoid mRCC receiving systemic therapy in subgroups divided by (a) extent of sarcomatoid features, (b) MSKCC risk classification, (c) Heng risk category and (d) first-line therapy.

Table 1

Summary of the largest retrospective series and prospective studies assessing sarcomatoid mRCC to date.

Author	N	Study Design	Regimens Assessed	Median Survival
Escudier *et al* [9]	25	Prospective phase II study	Doxorubicin/ifosfamide	3.9 months
Golshayan *et al* [12]	43	Retrospective single-institution study	VEGF-directed therapies (sunitinib, sorafenib, or bevacizumab)	11.8 months
Haas *et al* [8]	39	Prospective phase II study	Doxorubicin/gemcitabine	8.8 months
Kuroda *et al* [19]	30	Retrospective, single-institution study	VEGF-directed therapies, immunotherapy and chemotherapy	3.6 months
Pal *et al*	21	Retrospective single-institution study	VEGF-directed therapies, immunotherapy and chemotherapy	18.0 months

Table 2

Characteristics of the study population.

	***N* (%)**
Age	
Median (range)	54 (36–80)
Sex	
Male	17 (81%)
Female	4 (19%)
Histologic type	
Sarcomatoid	4 (19%)
Sarcomatoid + clear	13 (62%)
Sarcomatoid + other[a]	4 (19%)
Sites of disease	
Bone	5 (24%)
Brain	3 (14%)
Liver	8 (38%)
Lung	16 (76%)
Prior nephrectomy	20 (95%)
MKSCC risk status	
Good	1 (5%)
Intermediate	15 (71%)
Poor	5 (24%)
Heng risk group	
Good	1 (5%)
Intermediate	16 (71%)
Poor	4 (24%)
Sarcomatoid features[b]	
Predominant	13 (62%)
Non-predominant	8 (38%)

[a]Patients characterized as having “Sarcomatoid features + other” included patients with papillary (n=1), chromophobe (n=1), and unclassified (n=2) histology.

[b]Sarcomatoid predominant disease was characterized as patients having ≥ 20% sarcomatoid features indicated in available pathology reports.