

The Role of Metastasectomy in Patients with Renal Cell Carcinoma with Sarcomatoid Dedifferentiation: A Matched Controlled Analysis



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Abbreviations and Acronyms

CT = computerized tomography
IFN/IL-2 = interferon/interleukin-2
LN = lymph node
MRI = magnetic resonance imaging
OS = overall survival
RCC = renal cell carcinoma
RN = radical nephrectomy
sRCC = RCC with sarcomatoid dedifferentiation

Purpose: Management of metastatic renal cell carcinoma with sarcomatoid dedifferentiation remains a therapeutic challenge with no standard treatment strategies. We evaluated whether metastasectomy has any survival benefit in patients with metastatic sarcomatoid dedifferentiation treated with radical nephrectomy.

Materials and Methods: From an institutional database of 273 patients with sarcomatoid dedifferentiation treated with nephrectomy we matched 80 with synchronous and asynchronous metastases for age, ECOG (Eastern Cooperative Oncology Group) performance status, histology and lymph node status. Matched pairs were then retained only if patients who did not undergo metastasectomy were alive at metastasectomy comparable to matched surgical patients to decrease the bias of survival outcomes. Overall survival from nephrectomy was studied using univariable and multivariable proportional hazards regression.

Results: Median overall survival was 8.3 (95% CI 6.5–10.5) and 18.5 months (95% CI 11.5–42.9) in patients with synchronous and asynchronous metastases, respectively. Overall survival in patients who underwent metastasectomy for synchronous metastasis compared to nonsurgical patients was 8.4 and 8.0 months ($p = 0.35$), respectively. Similarly, overall survival in patients with asynchronous metastases treated with metastasectomy compared to the nonsurgical group was 36.2 and 13.7 months, respectively ($p = 0.29$). On multivariable analysis positive lymph nodes at nephrectomy were associated with an increased risk of death in the synchronous and asynchronous patient subgroups (HR 2.1, 95% CI 1.1–4.0, $p = 0.03$ and HR 3.3, 95% CI 1.2–9.2, $p = 0.02$, respectively).

Conclusions: In the current study there was no clear evidence of benefit in patients with sarcomatoid dedifferentiation who underwent metastasectomy after nephrectomy. Particularly, the group of patients with pathological lymph node positive disease at nephrectomy had considerably worse survival.

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APPROXIMATELY 30% of patients with RCC have metastatic disease at presentation and metastatic disease will ultimately develop in up to 40% who undergo RN for localized/locally advanced disease.¹⁻³ Patients with metastatic RCC have a poor 5-year survival rate of less than 20%.¹ In the last decade systemic management of metastatic RCC has significantly changed with increased understanding of the molecular biology of RCC. Agents that target the VEGF (vascular endothelial growth factor) and mTOR (mammalian target of rapamycin) pathways have revolutionized the treatment of advanced RCC. However, a complete response to systemic therapy alone is extremely rare and surgical resection of metastatic deposits is still valuable in well selected patients.⁴

Retrospective studies suggest that patients who undergo complete resection of isolated metastases tend to have better outcomes with 5-year survival rates between 35% and 65%.^{3,5-10} Favorable subgroups include patients with solitary metastases, those with a disease-free interval after nephrectomy of greater than 1 year, those with complete resection of metastases and younger patients.^{11,12} However, to our knowledge histopathological factors have yet to be studied for predicting outcomes in patients who undergo metastasectomy.

sRCC is a rare variant of RCC that accounts for 1% to 8% of all RCCs and can be observed across all RCC histological subtypes. Histologically, it consists of pleomorphic spindle cells and/or malignant-appearing giant cells interposed with a carcinoma component.^{13,14} sRCC is an aggressive tumor associated with a poor clinical course and a median survival of less than 1 year.¹⁵⁻¹⁸ Conventional cytotoxic chemotherapy and IFN/IL-2 immunotherapy only result in a minimal to moderate response and survival benefit.^{15,19} In addition, recent reports have shown that a higher percent of sarcomatoid component in sRCC correlates with a worse response to targeted therapy.^{19,20}

Despite recent advances in our understanding of the biology of advanced RCC, the management of metastatic sRCC continues to remain a therapeutic challenge with no standard treatment strategies. In this study our objective was to evaluate whether metastasectomy offers any survival benefit in patients with metastatic sRCC who were already treated with nephrectomy.

PATIENTS AND METHODS

The University of Texas M.D. Anderson Cancer Center institutional review board approved the current study.

From 1986 to 2011 we identified 273 patients who underwent nephrectomy and were diagnosed with sRCC. Patients with RCC and sarcomatoid features treated with nephrectomy were included in the main database. Patients diagnosed with sRCC subsequent to nephrectomy (ie at metastasectomy) with no metastatic disease, with a sarcomatoid percent of 100%, in unreported clinical trials, with a history of another metastatic malignancy or with incomplete followup information were excluded from study (fig. 1).

All patients in the metastasectomy groups underwent complete resection of the index organ(s) with no evidence of macroscopic disease after surgical resection. We defined synchronous metastatic disease as metastatic disease at initial presentation and nephrectomy, and asynchronous disease as new metastatic disease after nephrectomy in the absence of metastatic disease at the initial diagnosis of RCC. The location of metastases was classified as lung, bone, brain, viscera and other.

Recorded clinicopathological features included patient age, gender, race, ECOG performance status, Charlson comorbidity index, tumor pathology, regional LN involvement at nephrectomy, presence or absence of metastatic disease at nephrectomy and survival outcome. Staging was assigned using the 2010 AJCC (American Joint Committee on Cancer) classification.²¹

All patients underwent a metastatic evaluation, including chest x-ray or CT of the chest and CT or MRI of the abdomen and pelvis before original nephrectomy and/or metastasectomy. Bone scan and brain MRI were done as clinically indicated. Regional retroperitoneal LN dissection was performed at the discretion of the operating surgeon at nephrectomy. In the synchronous and asynchronous metastasectomy subgroups surgical resection was done primarily at disease sites amenable to complete resection. Adjuvant and/or salvage systemic therapy for synchronous metastasis or progression to metastasis after nephrectomy (asynchronous) was administered under the discretion of the treating physician. Surveillance after surgical resection typically consisted of CT of the chest, and CT or MRI of the abdomen and pelvis at regular intervals every 3 to 6 months after nephrectomy and/or metastasectomy.

Statistical Methods

Patients were matched in metastasectomy/non-metastasectomy pairs for ECOG performance status, age group (55 years or less vs greater than 55), histology, and pathological stage and nodal status at RN for synchronous and asynchronous metastases groups. Matching, balance checking, and Q-Q plots of the empirical distributions were performed using the MatchIt package^{22,23} in R, version 3.1.1 (<https://www.r-project.org/>). Furthermore, to control for patients who were not treated with metastasectomy because they did not live long enough, each matched pair was checked to confirm that the patient without metastasectomy lived at least until the time that metastasectomy was performed in the matching patient.

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