Complete Surgical Metastasectomy of Renal Cell Carcinoma in the Post-Cytokine Era

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Purpose: Data supporting complete metastasectomy of metastatic renal cell carcinoma were derived primarily from the era of cytokine therapy. Whether complete metastasectomy remains beneficial in patients who receive more recently approved systemic therapies has not been well studied. The objective of this study was to examine survival outcomes among patients treated with complete metastasectomy in the era of targeted therapy and checkpoint blockade availability.

Materials and Methods: We queried our institutional nephrectomy registry and identified 586 patients who underwent partial or radical nephrectomy of unilateral, sporadic renal cell carcinoma with a first occurrence of metastasis between 2006 and 2017. Of these patients 158 were treated with complete metastasectomy. Associations of complete metastasectomy with cancer specific and overall survival were assessed using Cox proportional hazards models.

Results: Median followup after the diagnosis of metastasis was 3.9 years, during which 403 patients died, including 345 of renal cell carcinoma. Of the patients treated with complete metastasectomy 147 (93%) did not receive any systemic treatment of the index metastatic lesion(s). Two-year cancer specific survival was significantly greater in patients with vs without complete metastasectomy (84% vs 54%, p <0.001). After adjusting for age, gender, and the timing, number and location of metastases complete metastasectomy was associated with a significantly reduced likelihood of death from renal cell carcinoma (HR 0.47, 95% CI 0.34–0.65, p <0.001).

Conclusions: Complete surgical resection of metastases of renal cell carcinoma was associated with improved cancer specific survival in the post-cytokine era. It may be considered in appropriate patients after a process of shared decision making.

Key Words: kidney neoplasms; carcinoma, renal cell; neoplasm metastasis; metastasectomy; mortality

Abbreviations and Acronyms

CM = complete metastasectomy
CSS = cancer specific survival
ECOG = Eastern Cooperative Oncology Group
MDT = metastasis directed therapy
mRCC = metastatic RCC
MRI = magnetic resonance imaging
OS = overall survival
RCC = renal cell carcinoma

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Complete surgical resection of RCC metastasis has been shown to be associated with a survival advantage compared to incomplete or absent metastasectomy.[1–5] Accordingly CM is endorsed by clinical practice guidelines in appropriately selected patients with mRCC.[6] However, most existing data supporting this strategy were derived from the cytokine era.[2] Whether CM remains associated with improved survival with the availability of more recently approved systemic therapies has not been well characterized. Furthermore, nonsurgical MDTs, including thermal ablation[7,8] and

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stereotactic radiotherapy,[9,10] have been increasingly performed to treat patients with mRCC, given demonstrated efficacy for local control.

However, we are not aware of any comparative data to support an improvement in CSS associated with MDT. Therefore, the objective of the current study was to examine survival outcomes among patients with mRCC with and without CM during an era when targeted therapy and checkpoint inhibitors were available. We also explored survival among patients with complete nonsurgical treatment of metastasis.

PATIENTS AND METHODS

Patient Selection

After obtaining Institutional Review Board approval (IRB No. 17-010685) we queried the Mayo Clinic Rochester Nephrectomy Registry to identify 607 adults 18 years old or older treated with radical or partial nephrectomy of unilateral, sporadic RCC between January 1970 and December 2015 in whom the first occurrence of distant metastasis was diagnosed between 2006 and 2017. These dates were chosen to correspond with U.S. Food and Drug Administration approval of sorafenib in December 2005, which was the first targeted agent available for RCC.[11]

The 14 patients in whom metastasis was identified at death as well as the 7 treated with neoadjuvant or adjuvant systemic therapies of localized (M0) disease at nephrectomy were excluded from study, resulting in a final cohort of 586 (fig. 1). Data are reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[12]

Features Studied

Demographics included patient age at the first occurrence of distant metastasis (ie the index metastasis) and gender. Nephrectomy features included surgical approach, tumor size, ECOG performance status, the Charlson Comorbidity Index (not counting the primary tumor or RCC metastasis), RCC subtype, 2018 pT and pN classifications, and grade. Index metastasis features included timing in relation to nephrectomy (synchronous, asynchronous 1 year or less, or asynchronous more than 1 year according to existing prognostic models),[13,14] the number of distinct metastatic sites, the location of metastases (pulmonary, nonregional nodes, bone, liver or other) and whether the patient underwent CM. All metastasis sites diagnosed within 6 weeks of the index metastasis were considered to have developed simultaneously.

Imaging to characterize metastasis was not standardized. However, computerized tomography and/or MRI is typically done to assess resectability. Brain MRI is obtained when clinically indicated. Bone metastasis is typically imaged with computerized tomography and MRI while bone scan and positron emission tomography are rarely performed.

Metastasectomy was defined as surgical resection within 90 days of the metastasis diagnosis. Complete metastasectomy was defined as complete resection of all index sites of metastasis. Nonsurgical MDT was defined as radiation, radio frequency ablation or cryoablation to a metastatic site within 90 days of metastasis. Complete nonsurgical MDT refers to nonsurgical treatments delivered to all sites of metastatic disease.

Statistical Methods

Continuous features are summarized as the mean ± SD when approximately normally distributed, and otherwise

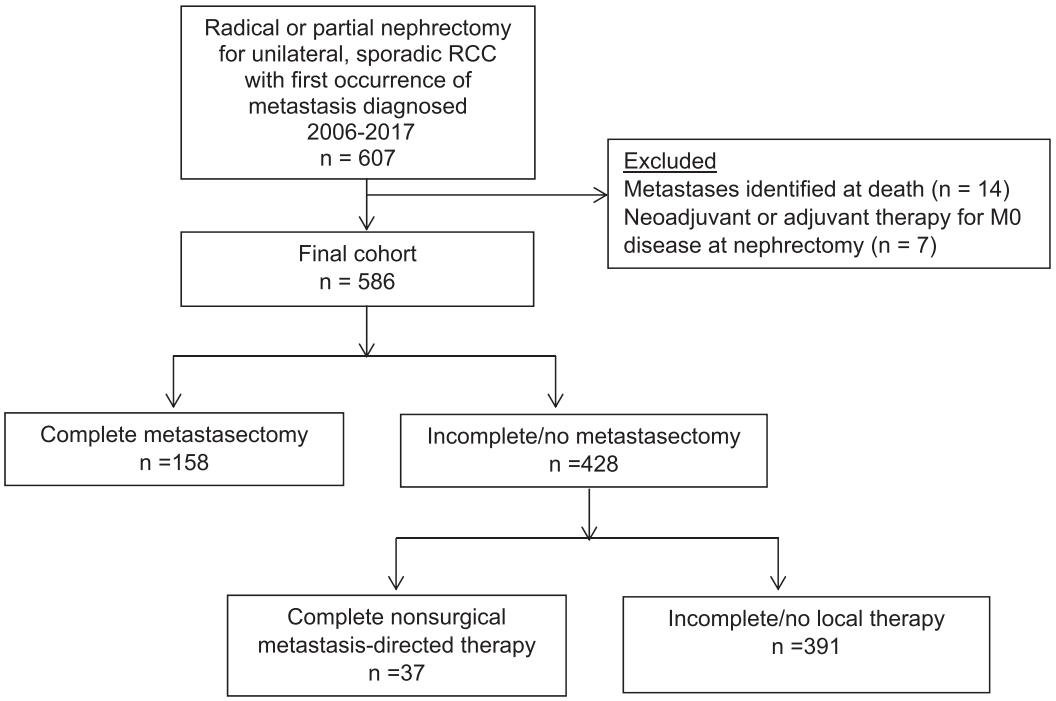

Figure 1. Flow diagram of cohort selection

as the median and IQR. Categorical features are summarized as the frequency count and percent. Features were compared in patients with vs without CM using the 2-sample t-test, and the Wilcoxon rank sum and chi-square tests. OS and CSS rates were estimated by the Kaplan-Meier method with followup calculated from the date of the index metastasis. Associations with time to death from any cause and time to death from RCC were evaluated using Cox proportional hazards regression models and summarized with the HR and 95% CI. Because ECOG status and the Charlson comorbidity index were assessed at nephrectomy and not reassessed at the time of metastasis, these features were not included in the Cox models.

Sensitivity analysis was performed which included ECOG status in the comparison of CM vs no CM as there was evidence it was not equally distributed between the groups ($p=0.07$). We also performed an exploratory analysis comparing complete nonsurgical MDT (but without CM) to incomplete or no local therapy (neither CM nor complete MDT) using Cox proportional hazards regression.

Statistical analyses were performed with SAS®, version 9.4. All tests were 2-sided with $p<0.05$ considered statistically significant.

RESULTS

Supplementary table 1 (https://www.jurology.com) lists baseline characteristics of the study cohort. In the 408 M0 cases at nephrectomy median time to the index metastasis was 2.3 years (IQR 0.5-5.7). By the last followup 403 patients had died, including 345 who died of RCC. The 29 patients who died of an unknown cause were excluded from CSS analyses. Median followup in the 183 patients who were still alive at the last followup was 3.9 years (IQR 2.3-6.7).

A total of 158 patients (27%) underwent CM. Table 1 shows features in patients with vs without CM. Of the 586 included patients the treatment was only CM in 140, only systemic therapy in 234, only MDT in 32, a combination of CM, MDT and/or systemic therapy in 43, and no systemic or local therapy in 137 in whom lesions were observed (supplementary table 2, https://www.jurology.com). Nonsurgical MDT in the 68 patients included radiation in 54, radio frequency ablation in 4, cryoablation in 9, and radiation and cryoablation in 1. Supplementary table 3 (https://www.jurology.com) summarizes the systemic therapies performed for the index metastases.

Of the 158 patients who underwent CM 147 (93%) did not receive systemic therapy of the index metastasis. Median OS in these patients was 7.2 years and median CSS was not reached. At a median of 1.6 years (IQR 0.7-2.5) 48 of these patients (33%) were treated with systemic therapy of subsequent metastases. Metastasis subsequently developed in 113 of the 158 patients (72%) treated with CM. Median subsequent metastasis-free survival following CM was 1.4 years. When stratified by metastatic disease at nephrectomy, median subsequent metastasis-free survival was 1.9 years in M0 cases and 0.6 years in M1 cases (supplementary fig. 1, https://www.jurology.com).

Table 1. *Demographics, nephrectomy performance status and features of index metastasis in patients with vs without complete metastasectomy*

	Complete Metastasectomy				
	No		Yes		p Value
No. pts	428		158		—
Mean ± SD age at metastasis	64.5 ± 11.5		64.7 ± 9.8		0.8
Median nephrectomy Charlson score (IQR)	0	(0-2)	0	(0-1)	0.2
No. male (%)	317	(74)	108	(68)	0.2
No. nephrectomy ECOG status (%):					
0	342	(80)	137	(87)	0.07
1	59	(14)	13	(8)	
2	16	(4)	6	(4)	
3	10	(2)	2	(1)	
4	1 (less than 1)		0		
No. metastasis timing (%):					
Synchronous with nephrectomy (M1)	123	(29)	55	(35)	<0.001
Asynchronous, 1 yr or less (M0)	132	(31)	13	(8)	
Asynchronous, greater than 1 yr (M0)	173	(40)	90	(57)	
No. distinct metastatic sites (%):					
1	232	(54)	143	(91)	<0.001
2 or More	196	(46)	15	(9)	
No. metastasis location (%):*					<0.001
Lung	265	(62)	50	(32)	
Bone	101	(24)	16	(10)	
Nonregional lymph nodes	106	(25)	9	(6)	
Liver	63	(15)	7	(4)	
All other locations	120	(28)	81	(51)	

* Patient could be included in more than 1 group.

CSS was significantly better in men treated with CM than in those treated without it (2-year CSS 84% vs 54%, $p<0.001$, fig. 2, *A*). Similarly, patients who underwent CM had significantly greater OS (2-year OS 81% vs 53%, $p<0.001$, fig. 2, *B*). When analyzed by site, CM was associated with significantly greater CSS among patients with only pulmonary metastasis (2-year CSS 89% vs 68%) as well as those with nonpulmonary metastasis (2-year CSS 82% vs 48%, supplementary fig. 2, https://www.jurology.com).

Table 2 lists multivariable associations of demographics and index metastasis features with time to death from any cause and death from RCC. After adjusting for patient age and gender, and the timing, number and location of metastases CM remained associated with a significantly reduced likelihood of death from RCC (HR 0.47, 95% CI 0.34−0.65, $p<0.001$). An assessment of 2-way interactions with CM indicated that the beneficial effect of CM on death from RCC was evident regardless of age, gender and the timing, number and location of metastases. Sensitivity analysis including the ECOG status of nephrectomy in the model had a negligible effect on the point estimate and CI of the association of CM with death from

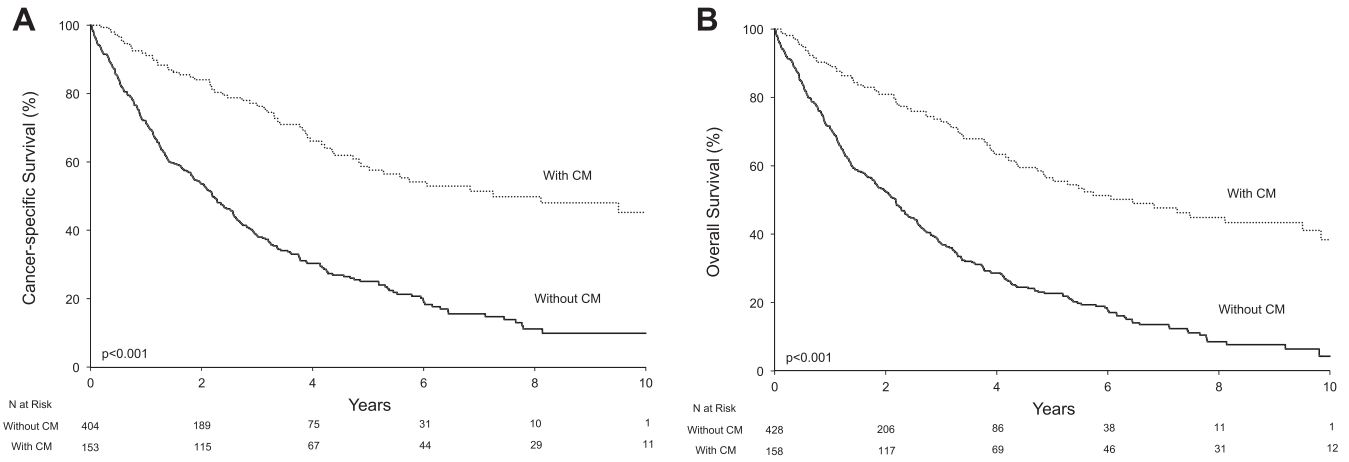

Figure 2. Survival rates in patients treated with vs without CM. *A*, CSS at 2, 4, 6, 8 and 10 years was 54%, 30%, 19%, 11% and 10% in men without CM, and 84%, 66%, 54%, 50% and 45%, respectively, in those with CM. *B*, OS at 2, 4, 6, 8 and 10 years was 53%, 29%, 18%, 9% and 4% in men without CM, and 81%, 63%, 51%, 45% and 38%, respectively, in those with CM.

RCC (HR 0.46, 95% CI 0.34–0.64, supplementary table 4, https://www.jurology.com).

Of the 57 patients with planned nonsurgical MDT but without CM 37 received completely nonsurgical treatment. Supplementary table 5 (https://www.jurology.com) shows a comparison of features in patients with complete nonsurgical MDT vs the 391 with incomplete or no local therapy. CSS in those with complete MDT was significantly greater than in those with incomplete or no local

Table 2. *Multivariable associations with time to death from any cause and death from RCC in patients with vs without CM and patients with complete MDT and incomplete and/or no local therapy*

	Any Cause Death		RCC Death	
	HR (95% CI)	p Value	HR (95% CI)	p Value
	CM vs no CM			
Age at metastasis	1.32 (1.19–1.47)*	<0.001	1.29 (1.16–1.45)*	<0.001
Male gender	0.98 (0.78–1.23)	0.8	0.89 (0.70–1.14)	0.4
Metastasis timing:				
Synchronous with nephrectomy (M1)	1.79 (1.39–2.31)	<0.001	1.89 (1.44–2.50)	<0.001
Asynchronous, 1 yr or less (M0)	1.69 (1.31–2.18)	<0.001	1.67 (1.34–2.32)	<0.001
Asynchronous, greater than 1 yr (M0)	1.0 (referent)	—	1.0 (referent)	—
No. distinct metastatic sites:				
1	1.0 (referent)	—	1.0 (referent)	—
2 or More	1.43 (1.04–1.98)	0.03	1.54 (1.10–2.16)	0.01
Metastasis location:				
Lung	0.91 (0.69–1.21)	0.5	0.92 (0.68–1.25)	0.6
Bone	1.48 (1.12–1.96)	0.006	1.39 (1.04–1.87)	0.03
Nonregional lymph nodes	1.47 (1.09–1.99)	0.01	1.56 (1.15–2.13)	0.005
Liver	1.45 (1.05–2.00)	0.02	1.42 (1.02–1.98)	0.04
All other locations	0.91 (0.69–1.20)	0.5	0.93 (0.70–1.25)	0.6
Complete metastasectomy	0.47 (0.35–0.63)	<0.001	0.47 (0.34–0.65)	<0.001
	Complete MDT + incomplete/no local therapy			
Age at metastasis	1.28 (1.14–1.43)*	<0.001	1.27 (1.13–1.44)*	<0.001
Male gender	0.95 (0.74–1.23)	0.7	0.87 (0.66–1.14)	0.3
Metastasis timing:				
Synchronous with nephrectomy (M1)	1.38 (1.03–1.84)	0.03	1.45 (1.06–1.99)	0.02
Asynchronous, 1 yr or less (M0)	1.53 (1.17–2.01)	0.002	1.60 (1.20–2.15)	0.002
Asynchronous, greater than 1 yr (M0)	1.0 (referent)	—	1.0 (referent)	—
No. distinct metastatic sites:				
1	1.0 (referent)	—	1.0 (referent)	—
2 or More	1.32 (0.94–1.86)	0.1	1.39 (0.97–2.00)	0.07
Metastasis location:				
Lung	0.90 (0.66–1.23)	0.5	0.94 (0.67–1.30)	0.7
Bone	1.56 (1.17–2.09)	0.003	1.47 (1.08–2.00)	0.02
Nonregional lymph nodes	1.50 (1.09–2.06)	0.01	1.57 (1.14–2.18)	0.007
Liver	1.43 (1.02–2.00)	0.04	1.38 (0.97–1.96)	0.07
All other locations	0.97 (0.72–1.32)	0.9	0.97 (0.71–1.34)	0.9
Complete nonsurgical metastasis directed therapy	0.67 (0.42–1.07)	0.09	0.62 (0.37–1.04)	0.07

* Represents 10-year age increase.

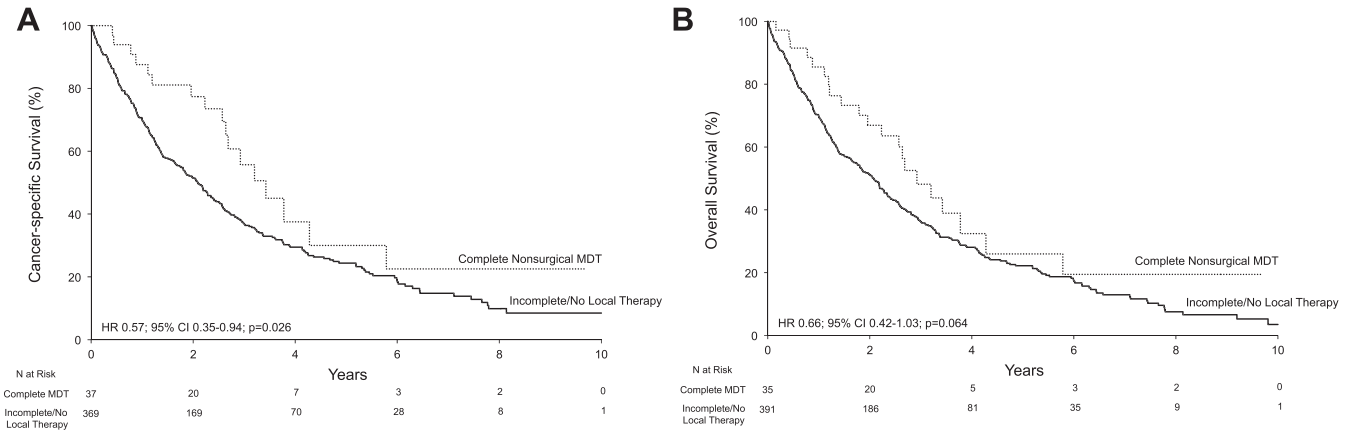

Figure 3. Survival rates in patients treated with complete nonsurgical MDT vs those with incomplete and/or no local therapy. *A,* CSS. *B,* OS.

therapy (fig. 3, *A*). OS also appeared greater in MDT cases, although this difference was not statistically significant (p=0.064, fig. 3, *B*). After adjusting for age and gender, and the timing, number and location of metastases complete MDT was not significantly associated with a decreased risk of death from RCC (HR 0.62, 95% CI 0.37–1.04, p=0.07) or death from any cause (HR 0.67, 95% CI 0.42–1.07, p=0.09, table 2).

Sensitivity analysis including nephrectomy ECOG status had a negligible effect on the point estimate and CI of the association of complete MDT with death from RCC (HR 0.61, 95% CI 0.36–1.04, supplementary table 6, https://www.jurology.com).

DISCUSSION

We observed that CM of mRCC was associated with improved CSS and OS compared to incomplete or no CM in the era of targeted therapy and checkpoint blockade availability. This association persisted after adjusting for the timing, location and number of metastases and it was observed in the context of 93% of patients who underwent CM but did not receive systemic treatment of the index metastasis. These data suggest that CM should continue to have a role in the management of mRCC despite the improved efficacy of targeted therapies[15–17] and checkpoint inhibitors[18] relative to previously available systemic agents.

Careful patient selection for this approach remains key. In this series most patients chosen for CM had a solitary metastasis and a prolonged disease-free interval between nephrectomy and metastasis development, consistent with known prognostic features of CM.[19] Moreover, a strategy of CM followed by observation, as in our study, has the potential advantage of sparing patients the additional morbidity of systemic agents while preserving the efficacy of these agents for use later in the disease process. However, whether a benefit exists for adjuvant systemic therapy after CM is the focus of ongoing trials.[20]

Multiple prior series support the usefulness of CM in the management of mRCC during the cytokine era. In a recent meta-analysis Zaid et al identified 8 studies of CM which enrolled patients treated from 1976 to 2013.[2] Only 2 of these studies included patients treated after 2008[21,22] while none evaluated patients exclusively treated in the era of targeted therapy. Thus, this may have biased the results of that report to overestimate the oncologic efficacy of CM.

In a separate study Tornberg et al reported a single institution experience in 97 patients treated with metastasectomy between 2006 and 2017, of whom 46 underwent CM.[23] Despite the small sample size the authors observed a significant improvement in OS and delayed time to initiation of targeted therapy in CM cases, findings in line with our findings. Similarly, Sun et al used the NCDB (National Cancer Database) to identify 1,976 patients treated with metastasectomy from 2006 to 2013.[24] They found that metastasectomy was associated with a 27% reduction in all cause mortality.

In the current study we observed a larger improvement in survival with all cause mortality reduced by nearly 60% among patients who underwent CM. This discrepancy in results between our study and that of Sun et al may be attributable to inability to discern whether metastasectomy was complete or incomplete in the latter study as patients who underwent any form of surgical resection of metastatic lesions were considered in aggregate.[24] Furthermore, limitations in that data set precluded an assessment of cancer specific mortality. In this regard our study builds on the findings of Sun et al by confirming an advantage to CM for cancer specific mortality in the era of contemporary systemic therapy.

Given that metastasectomy may be associated with a major complication rate as high as 28%,[25] there has been increasing interest in nonsurgical MDT to address RCC metastases. Welch et al reported the results of percutaneous thermal ablation of 82 mRCC lesions in a total of 61 patients, including an estimated 94% 2-year local recurrence-free survival rate and only 3 grade 3-4 complications.[7] Similar efficacy following cryoablation of mRCC lesions was noted by Bang et al, who reported major complication and local recurrence rates of 2% and 3%, respectively, at a median followup of 16 months.[8]

In addition to ablative techniques, stereotactic radiotherapy has also been investigated as treatment of mRCC. A single institution series of 84 patients with a total of 175 mRCC lesions demonstrated a 91% local control rate 1 year following stereotactic ablative radiotherapy with long-term grade 3 or higher toxicity observed in only 3% of patients.[10] A systematic review of stereotactic radiotherapy revealed similarly excellent local control rates of 92% for intracranial and 89% for extracranial mRCC.[9] However, despite the demonstrated local efficacy of these therapies, comparative survival with or without complete MDT remains under studied.

As an exploratory analysis we compared complete MDT to incomplete or no local therapy. While the CSS and OS comparisons did not reach the threshold of statistical significance, the CSS HR and CI suggested the potential for a significant relationship which our study did not have sufficient power to demonstrate (HR 0.62, 95% CI 0.37−1.04, $p=0.07$). It appears plausible that in a larger sample significantly improved survival associated with MDT may be detected. Due to the low sample size for the purpose of this analysis thermal ablation and radiotherapy were combined in a single MDT group and we recognize that the heterogeneity of this group limited our ability to draw clinically relevant conclusions.

Nevertheless, these findings are hypothesis generating and encourage further investigation to determine whether complete MDT can confer a survival advantage over that of systemic therapy. Until data in this arena mature it continues to be our practice to offer nonsurgical MDT to appropriately selected patients who are uninterested in, wish to avoid the morbidity of or are not candidates for complete surgical metastasectomy.

We acknowledge that this analysis is limited by nonrandomized treatment allocation and, therefore, the results are subject to selection bias. We addressed this by reporting analyses adjusted for several relevant clinical and pathological features, although it is likely that residual unmeasured confounding persists. A randomized trial would be ideal to address this shortcoming. However, given the relative rarity of this disease state and recent accrual difficulties in trials of cytoreductive nephrectomy in patients with mRCC,[26,27] it is unlikely that one will be completed in the near future. In the meantime, clinicians need to rely on observational data such as these to inform practice.

Another notable limitation is the lack of assessing functional or comorbidity status at the time of metastasis. These features are only assessed in our registry at nephrectomy. We acknowledge that declines in these parameters from when they were measured may have influenced treatment selection and outcomes but they could not be adjusted for. Similarly, laboratory data are not collected at the time of metastasis, precluding analysis based on the Heng or MSKCC (Memorial Sloan Kettering Cancer Center) prognostic scores.[13,14] Furthermore, targeted therapies comprise the majority of systemic therapies performed in this series. Checkpoint inhibitors will be more frequently applied in the future, although targeted therapies are poised to remain an integral component of combination systemic therapy.[28,29]

Lastly, reported results may not be widely generalizable as they represent experience at a single institution.

CONCLUSIONS

In this study we observed that complete surgical resection of RCC metastasis was associated with improved survival in the post-cytokine era. Metastasectomy may be considered in appropriately selected patients following a process of shared decision making.

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EDITORIAL COMMENTS

The authors analyzed CM in a contemporary patient set. As in previous reports on CM including other focal therapies, which we have systematically reviewed (reference 4 in article), this retrospective series suggests that patients with a single metastatic site or oligometastatic sites allowing for complete resection have less aggressive tumor biology than their counterparts in whom the clinical presentation did not justify metastasectomy. Therefore, these data, for which the risk of bias is high, should not be taken as proof that improved cancer specific survival was due to CM.

In addition, the authors report that metastasis subsequently developed in 72% of CM cases at a median of 1.4 years. We found a similarly disappointing cure rate following CM in a large international database analysis determining recurrence patterns and OS in association with Leibovich risk scores as part of a wider project to issue recommendations on followup protocols.[1] With at least 4 years of followup the results demonstrated that recurrence and progression following CM are rapid and frequent, especially in patients with metachronous metastases who were at Leibovich high risk at nephrectomy of initially localized disease.[1] Without randomized data, patient selection for CM remains challenging and the current results help counsel patients (reference 4 in article). While a randomized trial of CM vs observation is likely not feasible due to a lack of equipoise, we might gain practice changing information from ongoing adjuvant trials of atezolizumab or pembrolizumab vs placebo for which patients after CM are eligible (ClinicalTrials.gov NCT03024996 and NCT03142334).

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CM is recommended as curative therapy or to extend survival in patients with mRCC.[1] However, the role of CM remains unclear in the era of targeted therapy. The current authors investigated patients treated at a center with one of the highest volumes in the United States and report that CM improved patient survival even in the era of targeted therapy. Median metastasis-free survival was 1.4 years after CM, which greatly benefits patients because they can enjoy a longer drug-free interval.

However, certain concerns associated with metastasectomy cannot be ignored. 1) The recent introduction of immune checkpoint inhibitors definitely necessitates reassessment of the role of CM. 2) We have encountered a few patients in whom multiple lesions showed a mixed response from immune checkpoint inhibitors. The role of incomplete metastasectomy involving removal of unresponsive lesions needs to be clarified because patient survival is further extended. 3) Patient selection criteria need to be defined because morbidity rates are not always low (reference 25 in article).

Based on the current study we have presently elected to retain the same strategy in these patients. In view of the ethical concerns associated with this issue it is difficult to perform randomized trials to investigate the role of metastasectomy. Therefore, data collection from multicenter, real world medical settings is warranted in the future to conclusively establish the appropriateness of this procedure.

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REPLY BY AUTHORS

Determining whether to offer CM to a patient with mRCC remains a clinical challenge. In the absence of a randomized trial we must be honest about the limitations of currently available data, acknowledging that 72% of patients treated with CM experienced a subsequent recurrence and observed improvements in CSS may have been due to selection of patients with the most favorable disease biology.

Nevertheless, improved survival is not the only outcome worthy of consideration. We observed that 93% of patients who underwent CM were able to avoid systemic therapy of the index metastatic lesion(s) with a median time to subsequent metastasis of 1.4 years. Such an approach is supported by recently reported data from a phase III, randomized trial showing no improvement in disease-free survival for 1 year of adjuvant pazopanib vs placebo following CM.[1] Therefore, patients can be counseled that CM will likely enable them to delay systemic therapy until later in the disease course. After considering the morbidity attendant to each therapeutic modality and its potential impact on quality of life they may preferentially elect CM.

While some patients in the current series were treated with nivolumab, we agree that the appropriate role of CM in conjunction with checkpoint inhibitors remains to be clearly defined. We await the results of ongoing trials.

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