Review Article

The role of metastasectomy in the treatment of metastatic renal cell carcinoma

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The role of metastasectomy in metastatic renal cell carcinoma (mRCC) has been widely debated. Most clinical information regarding metastasectomy has been obtained from small retrospective studies that include heterogenous patient populations. It is unclear in what setting patients may confer the most clinical benefit. Moreover, a significant portion of clinical evidence suggesting additional benefit of metastasectomy is derived from a non-contemporary era, when interleukin-2, interferon-alpha, and limited number of tyrosine kinase inhibitors were the only available treatment options in addition to surgery. In efforts to answer these questions, we peruse the current literature of metastasectomy in mRCC by specific anatomical location, analyze the clinicopathological factors associated with metastasectomy outcomes, and discuss the potential role of metastasectomy as an adjunct to targeted therapy and immunotherapy.

Keywords: Renal cell carcinoma (RCC); metastasis; metastasectomy

Received: 10 June 2019; Accepted: 25 June 2019; Published: 28 June 2019.

doi: 10.21037/amj.2019.06.02

View this article at: http://dx.doi.org/10.21037/amj.2019.06.02

Introduction

Approximately 30% of renal cell carcinomas (RCC) present as stage IV disease and metastasize to a variety of anatomical sites throughout the body. Moreover, about two-thirds of the metastatic renal cell carcinoma (mRCC) cases present with more than one metastatic site, with being lung (45–60%), bone (30–40%), lymph nodes (20–30%), liver (20–30%), adrenal gland (about 8–10%) and brain (5–10%) the most common six metastatic sites (1,2). Generally, mRCC is a radiotherapy- and chemotherapy-resistant cancer (3), thus surgery has remained as one of the few therapeutic armamentarium against this lethal disease for long decades (4). Although there are multiple schools of thought regarding the role of metastasectomy in patients with mRCC, the fact is that at this point in time, there is not a definite catch-all answer for all mRCC patients (*Table 1*). It is known however that complete surgical metastasectomy, which is not always attainable, has improved outcomes compared to incomplete surgical metastasectomy and is significantly associated with a reduced risk of all-cause mortality (pooled aHR 2.37; 95% CI, 2.03–2.87; P<0.001) (5). This strong evidence supports the use of metastasectomy in mRCC when feasible.

A systematic review of eight studies also evaluated the role of local treatment in mRCC and reported that in patients who underwent complete metastasectomy, the overall survival (OS) and cancer-specific survival (CSS) were both significantly longer than in patients who had either incomplete or no metastasectomy [40.8 months, interquartile range (IQR) 31.6–48.0 *vs.* 14.8 months, 13.3–21.0, respectively] (6). Patients with lung, liver, and

Table 1 Outcomes data of metastasectomy by anatomical location

Site	Study	# Pts treated	Surgical technique	Median PFS	5-year OS	median OS (months)	CSS	Median follow-up (months)	Predictive factors	Limitations
Lung	Zhao *et al.* [2017]	1,447	Pulmonary metastasectomy	NR	43%	NR	NR	NR	Complete resection; number of metastases; resection margin; size of largest; metastases	Meta-analysis depends of quality of other studies; potential bias in extrapolation methods; potential publication bias; language bias
	Ohtaki *et al.* [2017]	84	Pulmonary metastasectomy	5-year RFS: 45.7%	Overall 59.7%; complete 62.3%	79.2	NR	NR	Tumor size <2 cm; clear cell histology; complete resection	Retrospective, multi-institutional study; long study period
	Baier *et al.* [2015]	237	Laser lung resection	NR	Complete 54%; incomplete 7%	Complete 69; incomplete 19	NR	NR	Complete resection; number of metastases	
Bone	Langerhuizen *et al.* [2016]	183	Metastasectomy (48%) Intralesional curettage (30%); stabilization (22%)	NR	25%	Metastasectomy 43; intralesional curettage 20; stabilization 27	NR	10	Enbloc resection with negative surgical margins	Retrospective methodology; use of social security death index; surgeries performed by 10 different oncologists over 25 years; insufficient sample size
	Du *et al.* [2016]	114	Resection (n=33); resection + targeted therapy (n=24); targeted therapy (n=40)	NR	NR	Overall 9.6 (95% CI, 5.5–13.6); resection 39.1 (95% CI, 13.9–64.2); resection+ TT: 31.8 (95% CI, 16.0–47.6); TT: 7.6 (95% CI, 5.8–9.3)	NR	24.1 (95% CI, 16.5–31.7)	Resection of bone metastases with targeted therapy, Bisphosphonate treatment	Small single center cohort—selection bias
Liver	Staehler *et al.* [2010]	88	Liver resection (n=68); comparison group (n=20)	NR	Resection 62.2%±11.4% (SEM); comparison 29.3%±22.0%	Resection, 142 (95% CI, 115–169); comparison 27 (95% CI, 16–38)	NR	26	Low grade RCC non-synchronous metastases	Selection criteria for patients not well defined

Table 1 (*continued*)

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Site	Study	# Pts treated	Surgical technique	Median PFS	5-year OS	median OS (months)	CSS	Median follow-up (months)	Predictive factors	Limitations
Pancreas	Grassi *et al.* [2016]	276	Surgery or radiotherapy (n=77); systemic therapy (n=256)	12 (95% CI, 10–14)	Overall 58%; local treatment 75%	Overall 73 (95% CI, 61–86); local treatment 106 (95% CI, 78–204)	NR	36 (95% CI, 20–69)	MKSCC/IMDC prognostic score; pancreatic local treatment	Lack of central pathology/radiology review; heterogeneity of patients
Retroperitoneal lymph node	Russell *et al.* [2016]	50	RPLN metastasectomy following nephrectomy	Overall 19.5; recurrence >12 mo 47.6	NR	NR	5-year: 79%	28 (IQR, 13.7–51.2)	Recurrence >12 months after nephrectomy	Retrospective, multicenter collaborative design
	Thomas *et al.* [2015]	102	RPLN metastasectomy	Median RFS: 23 (95% CI, 16.4–29.6)	NR	NR	5-year: 52%	NR	Pathological nodal stage at time of nephrectomy; maximal diameter of recurrence	Retrospective study
Brain	Wronski *et al.* [1996]	50	Primary tumor resection (n=47); brain metastasis resection (n=23)	NR	8.50%	31.4 (from primary diagnosis); 12.6 (from craniotomy)	NR	NR	Supratentorial brain metastasis; left sided primary tumor; lack of neurological; deficits prior to surgical resection	Retrospective study
Head/neck	Iesalnieks *et al.* [2015]	140	Thyroidectomy	5-year RFS: 77%	46%	NR	NR	34	Invasion of adjacent cervical structures; age >70; current or past evidence of metastases to non-endocrine organs	Heterogeneity in reporting; large number of institutions involved; over 30 years of data

ORR, objective response rate; PFS, progression-free survival; OS, overall survival; NR, not reported; IQR, interquartile range; RFS, recurrence-free survival; TT, targeted therapy.

pancreatic metastases conferred the most benefit from complete metastasectomy compared to the incomplete or no metastasectomy counterpart. Patients with complete lung metastasectomies had a median OS of 36.3 *vs.* 30.4 months for incomplete *vs.* 18.0 months for no metastasectomy (P<0.05) (6). In liver metastasis patients, complete metastasectomy patients had a median OS of 142 months (95% CI, 115–169) *vs.* 27 months (95% CI, 16–38) in patients who underwent incomplete or no metastasectomy (P=0.003) (6). Last, the pancreatic metastasis cohort also had a significantly longer 5-year OS in those who had a complete metastasectomy compared to the incomplete or no metastasectomy (88% *vs.* 47%; P=0.0263). Moreover, the patients having complete metastasectomy compared to incomplete or none had reported more relief from cancer-related pain (6), underscoring the palliative benefit of complete metastasectomy in patients with mRCC.

A similar study analyzed the location of metastasis to 5-year OS and found that the patients deriving the most benefit from complete metastasectomy were those with pancreatic metastasis with a 5-year OS of 72% (7). The least impactful metastasectomy location was seen in patients with brain metastasis with a reported 5-year OS of 12% (7). Other locations such as bone, liver, retroperitoneum, lung, and thyroid all ranged between a 5-year OS of 18–52% (7). Although several studies reported OS benefit in various metastasis locations, all of them were retrospective non-randomized comparative studies, raising several questions about its efficacy, safety and applicability in routine clinical practice. Nevertheless, there are currently many ongoing randomized clinical trials of metastasectomy, which may potentially consolidate or refine its role, as either single or adjunct to systemic therapy for mRCC (*Table 2*).

Prognostic factors

Recent advancements in molecular biology and genomic studies have identified four distinct molecular subtypes of clear cell RCC (ccRCC). Each of them (ccRCC1, ccRCC2, ccRCC3, and ccRCC4) have demonstrated distinct prognostic and clinical features. Moreover, they appeared prognostic in selection of patients with mRCC for systemic therapy as molecular subtypes of ccRCC2 and ccRCC3 were associated with better objective response (OR) to first-line pazopanib (50%) than ccRCC1 (30%) and ccRCC5 (0%) subtypes. Of note, this classification system of ccRCC subtypes was significantly better at predicting progression-free survival (PFS) and OS than the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score on univariate analysis (8). Similarly, a second study from the same group assessed the prognostic impact of molecular subtypes of ccRCC on complete metastasectomy. The subtypes ccRCC1 and ccRCC4 were shown to be at greater risk of early relapse following metastasectomy [median disease-free survival (DFS) of 9 months] than subtypes of ccRCC2 and ccRCC3 (median DFS of 23 months). The reported median CSS was 133 months for subtypes ccRCC2 and ccRCC3 compared to 50 months for subtypes ccRCC1 and ccRCC4 (HR 2.7; P<0.001).(9) As molecular subtyping of ccRCC becomes more accurate and reproducible with standard methods, the prognostication of patients' trajectory and thus treatment decisions will likely to be more straightforward for patients with mRCC.

In addition to molecular subtype, some clinicopathological factors were found predictive for CSS in patients who underwent complete metastasectomy for mRCC. In a retrospective analysis of single-institutional cohort of 138 patients with a recurrence-free survival (RFS) and CSS of 27% and 84% at 5 years following metastasectomy, maximum tumor size at metastasectomy was associated with decreased CSS (HR 1.18 per 1 cm; P=0.001) (10). Further, sarcomatoid histology at nephrectomy was associated with decreased CSS than those without (HR 3.70; P=0.037) (10). Similarly, a bi-institutional study that included 109 patients who underwent partial or radical nephrectomy and at least one metastasectomy for mRCC identified five independent adverse prognostic features (T stage ≥3 of the primary tumor, Fuhrman grade ≥3 of the primary tumor, presence of non-pulmonary metastases, disease-free interval ≤12 months, presence of multiorgan metastases) and stratified all patients into four distinct prognostic subgroups (A-D) (11). The 5-year CSS for patients who had more than one metastasectomy compared to those with only one metastasectomy was significantly longer at 76% *vs.* 35%, respectively (P=0.005) (11). Moreover, a significant advantage to CSS with consecutive metastasectomies was noted (HR 0.4; 95% CI, 0.16–0.75; P=0.008) (11). Using this stratification method, there were significantly differing 2- and 5-year CSS rates: group A (0–1 risk factors) reported 95.8% and 83.1%, group B (2 risk factors) reported 89.9% and 56.4%, group C (3 risk factors) reported 65.6% and 32.6%, and group D (4–5 risk factors) reported 24.7% and 0% (P<0.0001) (11). Thus, both aggressiveness of tumor biology as well as the performance of metastasectomy seem to have significant impact on survival of the patients with mRCC. Further management options

Table 2 Ongoing clinical trials for neoadjuvant and adjuvant metastasectomy in mRCC

Therapy type	Study identifier	Phase	Intervention	Duration	Patients	Study start date	Study end date	Primary outcome measures
Metastasectomy alone	NCT00918775	Phase 2	Follow-up/evaluation during and after metastasectomy	Every 6 months up to 5 years	120 participants with RCC	June 09, 2009	June, 2021	24-week progression free/ relapse free survival rate
Neoadjuvant + metastasectomy	NCT03494816	Phase 2	Axitinib 5, 10 mg orally	8 weeks prior to metastasectomy	20 patients with metastatic and non-metastatic RCC with venous invasion	Dec 2017	June 2020	Improvement in Mayo classification
	NCT02595918	Phase 1	Nivolumab IV, metastasectomy, nephrectomy	Days 56, 42, 28, and 14 prior to metastasectomy	29 patients with clear cell RCC	May 19, 2016	Apr 30, 2020	Feasibility of 3+ doses of nivolumab and surgery without significant delay (>112 days)
	NCT02210117	Early Phase 1	Nivolumab IV alone *vs.* Nivolumab IV with bevacizumab or ipilimumab	Every 2 weeks for 6 weeks; metastasectomy after 4 weeks	105 patients with clear cell RCC	Nov 25, 2014	Nov 30, 2020	Safety and tolerability of therapy
Neoadjuvant + metastasectomy + adjuvant	NCT03473730	Early Phase 1	Daratumumab IV, Biopsy, Nephrectomy, Metastasectomy	Treatment for 8 weeks, ending at least 2 weeks prior to metastasectomy/ nephrectomy/biopsy; restart treatment 4–6 weeks after metastasectomy	30 patients with bladder cancer or RCC	May 29, 2018	Dec 31, 2021	Incidence of adverse events
Metastasectomy + adjuvant	NCT01444807	Phase 2	Sorafenib 400 mg orally	52 weeks or until recurrence of disease	132 patients completing metastasectomy	Dec, 2011	Sep, 2019	Recurrence free survival

can be based on presence of aggressive features and feasibility of surgical resection for patients. Currently, the National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer recommends surgical metastasectomy for patients with oligometastatic disease (or ablative techniques of metastasis for surgically unfit) during the same time with cytoreductive nephrectomy or at different times (12).

Lung metastasectomy

A meta-analysis including 1,447 patients who had undergone lung metastasectomy for mRCC showed that the 1-year OS was 84%, 3-year OS was 59%, 5-year OS was 43%, and 10-year OS was 20% in patients who had lung metastasectomies (13). This study additionally noted that incomplete metastasectomy was the single most significant prognostic factor for survival in these patients (HR 3.74; 95% CI, 2.49–5.61; P=0.000) (13). The latter finding corroborating the idea that complete metastasectomy is superior for patient outcomes to incomplete metastasectomy.

Moreover, histology of metastatic pulmonary lesions is predictive for survival after metastasectomy. In a multicenter retrospective study, the 78 patients who underwent complete pulmonary metastasectomy had a 5-year OS of 59.7% (14). This study found that tumor size <2 cm (HR 0.31; 95% CI, 0.13–0.78; P=0.012), clear cell type histology (HR 0.37; 95% CI, 0.16–0.83; P=0.025), and complete metastasis resection (HR 0.27; 95% CI, 0.10–0.78; P=0.015) were predictive for survival (14). In a retrospective study that assessed the utility and value of pulmonary parenchyma-saving technique, 237 mRCC cases with a mean number of 13 pulmonary metastasis were treated with laser resection for multiple pulmonary metastases (15). When the patients were stratified by number of pulmonary metastasis resected, the 5-year survival rates for patient with 1, 2–5, 6–9, 10–29, or 30–110 pulmonary metastases resected were 62%, 59%, 60%, 43%, and 40%, respectively (15). Thus it was suggested that parenchyma-saving techniques, such as laser resection, could even enable removal of high numbers of pulmonary metastases and provide comparable long-term survival unless complete resection was achieved (15). Nevertheless, in all studies, the reported 5-year OS rates of patients who underwent metastasectomy for pulmonary metastasis were around 50%, ranging from 45% to 60%, however 5-year OS was significantly decreased to less than 10% for patients treated with incomplete metastasectomy (13-15), underscoring the importance of achieving complete resection of pulmonary metastatic lesions for maximum survival benefit.

Bone metastasectomy

A retrospective study analyzed the recurrence rate and 1-year survival probability in 183 patients with RCC metastases to the appendicular skeleton. The recurrence rate at 1-year after metastasectomy was 13% compared to 22% and 39% after intralesional curettage and stabilization only (by intramedullary nailing or plate), respectively (P=0.003) (16). Additionally, the 1-year survival probability in patients who underwent bone metastasectomy was significantly higher than the other cohorts (P=0.020) (16). Having negative margins not only portended a lower recurrence rate (P<0.001); but also was associated with a significant survival benefit (P<0.001) (16). Of note, there were significant limitations to this non-randomized retrospective study since the proportion of patients with concurrent visceral metastases and highly disseminated disease were significantly lower in the metastasectomy subgroup. Secondly, postoperative radiation was more commonly given to the groups who underwent intralesional curettage (33%) and stabilization only (59%), as compared to metastasectomy (8%) (16).

The use of metastasectomy in bony metastatic disease was also reviewed in a retrospective study consisting of 114 patients. Single bone metastasis was noted in 68 (59.6%) patients; whereas, 46 (40.4%) patients had multiple bone metastases ranging between 2 and 5 (17). The localization of bone metastasis were in the axial bones (spines, skulls, and ribs) among 47 (41.2%) patients, in the appendicular skeletons (extremities, pelvis, clavicle, and scapula) among 20 (17.5%) patients and in 33 (28.9%) patients with a combination of both, whereas in 14 (12.3%) the exact locations was unknown (17). Patients treated with bone metastasectomy and targeted therapy compared to those treated with targeted therapy alone conferred a survival advantage with a longer median OS of 31.8 months (95% CI, 16.0–47.6) *vs.* 7.6 months (95% CI, 5.8–9.3), respectively in this cohort (17). Sarcomatoid features and high Fuhrman grade were unfavorable factors for OS; however, neither site nor number of bone metastasis had significant impact on OS (17). Moreover, the NCCN guidelines also recommend using bone-modifying agents such as bisphosphonates and RANKL inhibitors in order to avoid skeletal-related events such as bone fractures and spinal cord compression and radiation therapy for palliation; although their potential OS benefit remains undefined in

mRCC patients who have bone metastasis (12).

Pancreas metastasectomy

There is evidence that pancreatic metastases have a protective effect in mRCC. In a retrospective review of 228 patients with mRCC to the pancreas, the reported median OS was 39 months (95% CI, 24–57; P=0.02) compared to 26 months (95% CI, 21–31) for those without pancreatic metastases (P<0.01) (18). This study further found that CSS was longer in the pancreatic metastases group compared to the patients without pancreatic metastases of 42 *vs.* 27 months (P=0.05) (18). Additionally, this study found that patients who underwent nephrectomy (HR 0.54; 95% CI, 0.42–0.88; P=0.01) and had surgically negative margins (HR 0.49; 95% CI, 0.25–0.88; P=0.03) had a significant survival advantage (18). This study sheds light on the potentially less aggressive biology of mRCC that have a pancreatic predilection of metastasis.

In efforts to augment patient outcomes, a multicenter retrospective study of 276 patients with pancreatic metastasectomy were categorized by either being treated with targeted therapy or local therapy (surgery, radiotherapy, radiosurgery). The patients who were treated with targeted therapy had a median PFS of 12 months (95% CI, 10–14), a median OS of 73 months (95% CI, 61–86), and a 5-year OS of 58% (19). This was in contrast to those who underwent local therapy attaining a median OS of 106 months (95% CI, 78–204) and a 5-year OS of 75% (19). Additionally, this study found that IMDC score, undergoing nephrectomy, and having pancreatic local treatment were independent prognostic indicators for OS. Patients with IMDC score intermediate *vs.* good and poor *vs.* good had HRs of 1.45; 95% CI, 0.94–2.23 and HR 2.76; 95% CI, 1.43–5.35; P=0.0099, respectively (19). Those who underwent nephrectomy also had significantly improved prognosis (HR 5.31; 95% CI, 2.36–11.92; P<0.0001) (19). Last, who had local pancreatic treatment had a lower HR of 0.48; 95% CI, 0.30–0.78; P=0.0029 (19). Both data sets showed that patient population derived clinical benefit from metastasectomy over and above the confounding better prognosis that patients with pancreatic metastases inherently have.

Liver metastasectomy

The utility of metastasectomy in mRCC was further dissected in the context of liver metastases. A retrospective analysis of 88 patients found a significantly larger 5-year OS rate and longer median survival (MS) in patients who underwent liver metastasectomy compared to historical controls who did not. This study found that liver metastasectomy conferred a 5-year OS rate of 62.2% and MS of 142 months compared to the controls who did not have surgery experiencing a 5-year OS rate of 29.3% and MS of 27 months (P=0.003) (20). This study shows that there may be significant benefit for metastasectomy in patients with liver metastases; however, this may not be scot-free.

In a study that compared 1,102 patients with multiple organ metastasectomies, 19% of patients [209] had liver metastases resected. When compared to lung, bone, lymph nodes, adrenal glands, and brain metastasectomies, liver metastasectomy was significantly associated with the highest overall likelihood of complications compared to all other sites (odd ratio 2.59; 95% CI, 1.84–3.62; P<0.001) (21). This finding, although done with survival improving intent, shows that metastasectomy can carry significant risk, but also significant benefit.

Retroperitoneal lymph node (RPLN) metastasectomy

In a multicenter study of 50 patients following nephrectomy, the median duration until RPLN recurrence was 12.6 months (IQR, 6.9–39.5). Upon recurrent disease, these patients underwent RPLN metastasectomy and had a median PFS of 19.5 months with a 3-year PFS rate of 40.5% and a 5-year PFS rate of 35.4%. Additionally, the authors reported that having recurrence in the RPLNs within the first 12 months post-nephrectomy was associated with a lower median PFS compared to RPLN recurrence after 12 months from time of nephrectomy, 12.3 *vs.* 47.6 months (P=0.003), respectively. Last, there was a significantly higher risk of ensuing disease progression in those who recurred after a shorter duration (HR 3.51; P=0.005) (22). This study shows the importance of considering RPLN metastasectomy in patients who recur after primary nephrectomy.

In a retrospective study of 102 patients with RPLN metastases, Thomas *et al.* evaluated the role of RPLN metastasectomy in improving RFS and CSS. The authors found that in patients who underwent RPLN metastasectomy, the median RFS was 23 months (95% CI, 16.4–29.6). This study also reported the CSS rates at 1-, 3-, and 5-year being 92%, 71%, and 52%, respectively, with a median CSS of 66 months (95% CI, 29.9–102.1). The two most significant risk factors for CSS post-metastasectomy were node stage at initial nephrectomy (HR 4.08; 95% CI,

1.89–8.83; P<0.001) and largest dimension of the metastatic tumor (HR 1.21; 95% CI, 1.12–2.32; P<0.001), independent of one another (23). The impact RPLN metastasectomy can have on patients' RFS and CSS is significant and should help to inform decisions for patients who recur after initial nephrectomy.

Brain metastasectomy

In mRCC, brain metastasis is associated with poorer prognosis compared to other common metastasis such as lung or bone. In a retrospective cohort that included 50 mRCC patients who underwent craniotomy for brain metastasis, MS from primary diagnosis and from resection of brain metastasis were 34 and 12.6 months (24). Of note, five patients who died within 1 month of craniotomy were not included in the survival analysis. Craniotomy is also associated with significant co-morbidity as among the remaining 45 patients, 6 patient had reoperation due to cerebral edema or subdural hematoma, 7 patients had neurological deficits, and 1 patient had bacterial meningitis. The 1-year survival was ~50%, while 5-year survival was below 10% (24). The MS of the 8 patients with infratentorial (cerebellar) metastasis was significantly worse (3.0 months) than 42 patients with supratentorial metastases (P=0.0002) (24). Of note, lung was involved in about 75% [37] of the patients, and thoracotomy and resection of concurrent pulmonary metastasis was associated with improved survival outcomes in patients with brain metastasis of mRCC.

There are other nonsurgical treatment alternatives for patients with mRCC as well, whole-brain radiotherapy and stereotactic radiosurgery are being the two most common. Actuarial 2-year local control rate was reported as 55.2% in a retrospective analysis that consisted of 35 mRCC patients with brain metastases who underwent radiotherapy (25). Of note, focal stereotactic radiotherapy (in 10 patients) seemed to offer better tumor control and prolonged survival over the surgery and subsequent conventional radiotherapy (in 11 patients) with reported MS rates of 25.6 *vs.* 18.7 months, respectively (25). Therefore, unlike patients with other visceral metastases of RCC, radiation therapy appears as a viable alternative treatment option for patients with brain metastasis in addition to surgery.

Thyroid metastasectomy

In head and neck region, mRCC presents as either a confined metastasis to thyroid gland (75%) or a locally invasive tumor extending from thyroid gland through the neighboring structures (25%) (26). The latter phenotype is associated with poor survival and increased risk of local recurrence following thyroidectomy. In an analysis of 130 patients with thyroid gland metastasis, the 5-year OS rate of the patients who underwent thyroidectomy for thyroid metastasis was noted as 46% after a median follow-up of 34 months (26). About 30% of the patients developed local neck recurrence. In multivariate analyses, invasion of adjacent cervical structures were predictive for both inferior OS (HR 3.2; P=0.001) and local recurrence (HR 12.1; P<0.0001) (26). Of note, 23% and 13% of the patients also had concurrent pancreatic and adrenal metastases (26). The past evidence or concurrent metastases to non-endocrine organs (HR 2.4; P=0.003) and patient age over 70 years (HR 2.5; P=0.004) was other poor prognostic factors for OS (26).

Atypical metastasis of RCC

In a single institutional review of 1,800 surgically treated renal cancer cases, 27 cases with unusual metastasis were identified; eight in skin, six in muscles, four in testicle, three in nasopharynx, two in vagina, one in stomach, breast, spleen and omentum (27). The six metastases in thyroid and four in pancreas were also defined as atypical by the authors (a total of 37 atypical metastatic sites) and 57 other cases were operated for lung metastasis within the same cohort (27). In 32% of patients, atypical metastasis were detected at initial diagnosis, whereas metachronous atypical metastasis occurred after a mean of 53 months following initial diagnosis (27). After a mean follow-up of over 40 months, the efficacy of metastasectomy for atypical locations was found comparable to that for lung metastasectomy, as well as CSS (log-rank test, P=0.626) (27). Although this study with such low number of cases and short follow-up was underpowered, it can be suggested that patients presenting with unusual metastasis of renal cancer should be evaluated for metastasectomy if surgically possible.

Neoadjuvant & adjuvant systemic therapy with metastasectomy

For a long period of time, immunotherapy with interleukin-2 and targeted therapy have been the mainstay treatment for mRCC (4). The value of metastasectomy in combination with targeted therapy was evaluated in a few retrospective studies, and its role at these treatment settings remains more elusive. In a small multi-institutional cohort of 22

patients who underwent consolidative metastasectomy after targeted therapy (sunitinib, sorafenib, bevacizumab, ABT-510 alone or in different combinations with interleukin-2 or interferon-alpha), 21 patients were alive and one patient died of mRCC after a median follow-up of 27 months after metastasectomy (28). Of note, prior to metastasectomy, four patients demonstrated partial response (28). Metastasectomy sites were retroperitoneum in more than half of the patients (12), whereas lung in six, adrenal gland in two, bowel in two, and mediastinum, bone, brain and inferior venal caval thrombus in one patient each (28). Eleven patients (50%) developed a recurrence at a median follow-up of 42 weeks following surgery and four patients had postoperative complications within 3 months after surgery, although resolved with appropriate management (28). Although type and duration of targeted therapy showed significant variation among patients in this small cohort, metastasectomy after neoadjuvant targeted therapy appeared feasible with acceptable safety profile.

Additionally, a retrospective review included 34 patients with surgically complex metachronous metastasis or local recurrences. Targeted therapy was given to all of them as complete resection had seemed likely to be achieved by their physicians (29). The mean length of pretreatment with targeted therapy was 6 months [2–56], and site of recurrence were local in 16 patients and lymph node, lung, liver and adrenal in 11, 5, 8 and 5 patients, respectively (29). The probability of proceeding with local therapy was 85.3% and median OS of 29 patients treated with neoadjuvant therapy plus metastasectomy was 67 months (29). Overall, the median time without systemic therapy was 12 months (29).

Moreover, currently available few studies suggest an additional therapeutic value from treatment with metastasectomy prior to adjuvant targeted therapy in mRCC. Timing of targeted therapy appeared crucial as immediate targeted therapy after complete surgical resection of metastatic lesions was associated with a better median PFS among 53 patients with good and intermediate-risk mRCC (30). Although it was not associated with improved CSS, the relapse rate after immediate posy-operative targeted therapy was 26.3% (in 5 out of 19 patients) (30). In 30 patients who relapsed following targeted therapy regardless of timing of targeted therapy, objective response rate (ORR) was about 40% and disease control rates reached 85% (30). One comparative study grouped a total of 325 patients into three different groups as complete metastasectomy with targeted therapy [33], incomplete metastasectomy with targeted therapy [29], and only targeted therapy groups [263]; and demonstrated significant median PFS advantage in favor of first group (29.5, 18.8, *vs.* 14.8 months, P<0.001) (31). The median OS were 92.5, 29.6, and 23.5 months in the complete, incomplete, and non-metastasectomy groups (P<0.001), underscoring its potential therapeutic effect (31). Of note, metachronous metastasis, sarcomatoid feature, multiple metastasis, poor IMDC risk group and targeted treatment with mTOR inhibition (*vs.* VEGF inhibition) were also associated with decreased OS in this study (31).

Immunotherapy with immune checkpoint inhibitors (ICI) recently emerged as an effective systemic treatment option for mRCC. The ORR in patients with intermediate and poor-risk clear cell mRCC who were treated with nivolumab and ipilimumab was 42% and median PFS was 11.6 months (32). The efficacy of ICI is currently being tested in several ongoing clinical trials of mRCC as well. Despite the promising therapeutic outcomes of ICI, there are several challenges to overcome in management of mRCC, such as management of non-clear cell renal cancer and variant histology like sarcomatoid or of patients unable to tolerate systemic treatments. Likewise, the efficacy of ICI is limited in metastatic papillary renal cell carcinoma (mPRCC), which is the most common non-clear histology, especially in type 2 mPRCC (ORR of 15%; time to treatment-failure 3 months) (33). Thus, metastasectomy can still remain a valuable therapeutic tool adjunct to systemic treatment options for management in a particular subset of patients with mRCC. Currently there are many ongoing randomized clinical trials of metastasectomy, either alone or in combination with sorafenib, axitinib, nivolumab, or bevacizumab at neoadjuvant or adjuvant settings (*Table 2*). These trials might potentially consolidate or refine the role of metastasectomy in management of mRCC.

Conclusions

Although the rationale for local treatment is quite questionable and systemic treatments are standard of care for the majority at metastatic settings, metastasectomy appears to be a feasible treatment that increases the odds of OS in selected patients with mRCC. The growing body of knowledge in the literature also suggests that metastasectomy provides the most survival benefit in cases that complete resection is achieved and in cases with lung metastasis with the 5-year OS rates of around ~50% (1,2). However most clinical evidence has come from small retrospective single institutional studies and the efficacy and safety of metastasectomy needs to be further elucidated

in a metastatic site/organ-specific manner. Likewise, the perioperative risks of metastasectomy have to be weighed against the potential benefits in routine clinical practice. In the last decade, many targeted therapy and immunotherapy options for mRCC have emerged and become a standard of care, therefore metastasectomy might find a place as a part of a combination therapy rather than monotherapy for management of mRCC. As combination of available treatments might possibly provide better and more durable ORR for patients with mRCC, the results of the ongoing clinical trials that sequenced metastasectomy and systemic treatments are eagerly awaited.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2019.06.02). Dr. Spiess serves as an unpaid Associate Editor-in-Chief of *AME Medical Journal* from Sep 2017 to Feb 2020. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj.2019.06.02
Cite this article as: Adashek JJ, Aydin AM, Kim P, Spiess PE. The role of metastasectomy in the treatment of metastatic renal cell carcinoma. AME Med J 2019;4:30.

