The Evolving Role of Metastasectomy for Patients with Metastatic Renal Cell Carcinoma

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KEYWORDS

• Metastasectomy • Metastatic renal cell carcinoma • Thermal ablation • Radiation • Immunotherapy • Targeted therapy • Prognostic factors • Immune checkpoint inhibitors

KEY POINTS

- Surgical metastasectomy may enable periods of systemic treatment-free survival in well-selected patients.
- Ideal patients for metastasectomy are not frail and have a small volume of metastatic disease without aggressive pathologic features.
- The risk of morbidity associated with surgery depends on multiple factors and must be balanced with potential benefits from surgery.
- Prior to metastasectomy, patients should have a multidisciplinary evaluation, including surgeons and medical oncologists, to provide the best shared decision making.

INTRODUCTION

In 1939, Barney and Churchill[1] reported no recurrence of disease for 5 years after a patient was treated with nephrectomy for adenocarcinoma of the kidney and subsequent lobectomy for a 6-cm lung metastasis that was resistant to radiation therapy. Other historical case reports demonstrate that metastasectomy occasionally resulted in long-term survival for patients with metastatic renal cell carcinoma (mRCC), despite having no effective options for systemic therapy in this era.[2] In 1967, Middleton[3] reported 41 patients who had nephrectomy despite known metastatic disease treated from 1932 to 1965 at New York Hospital. The reported overall survival was significantly better for patients with solitary metastasis, most of whom were treated with metastasectomy. Long-term survivors included a patient, who was alive without recurrence, 31 years after the initial nephrectomy and 14 years after excision of a brain metastasis.

The rare opportunity to provide long-term, disease-free survival for a subset of patients with solitary metastasis provided a rationale for metastasectomy before active systemic treatments became available. More recently, patients with oligometastatic renal cell carcinoma (RCC) have been treated with metastasectomy after partial responses to cytokine therapy[4] or targeted therapies.[5] However, the benefit of surgery as a local treatment for RCC metastases is difficult to measure accurately because benefits are confined to a small fraction of patients and no large randomized clinical trials having investigated metastasectomy for typical mRCC patients. Furthermore, surgeons intentionally choose lower-risk patients with slow-growing metastases

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for metastasectomy, creating an observation bias when comparing outcomes.

Over the past 2 decades, systemic treatments that target angiogenesis or cell growth pathways have demonstrated prolonged survival compared to patients treated with interferon-α in large randomized clinical trials.[6,7] Although better systemic treatments for mRCC became increasingly available, the utilization of metastasectomy continued to increase from 2006 to 2013.[8] More recently, single-agent[9] or combination therapies[10] that target immunologic checkpoints have emerged as first-line systemic therapies. In 2019, new combination treatments using both targeted therapies and immune checkpoint inhibitors gained approval for mRCC treatment after demonstrating improved survival in clinical trials.[11,12] Metastasectomy may be less utilized with complete responses, which are more common with newer therapies (9% complete response rate for patients treated with nivolimab plus ipilimumab).[10] Metastasectomy, however, is likely to continue to play a role in the multidisciplinary treatment of mRCC until systemic therapies produce complete and durable responses. The purpose of this review is to examine the currently available data for metastasectomy in mRCC patients, including site-specific data and strategies for patient selection.

UTILIZATION OF METASTASECTOMY FOR METASTATIC RENAL CELL CARCINOMA

Studies that estimate how often mRCC patients are treated with metastasectomy were uncommon before the development of large cancer registries. Furthermore, improvements in imaging technology during the past few decades have resulted in earlier detection of smaller asymptomatic metastases, which also may have an impact on the utilization of metastasectomy,[13] which also may vary significantly among institutions. For example, in a single-institution series of 887 mRCC patients from 1976 to 2006, 48% of patients had surgical resection of metastases.[14] Sun and colleagues[8] evaluated population-level data from the National Cancer Database and found 1976/6994 (28%) patients with mRCC were treated with metastasectomy from 2006 to 2013 and that utilization increased from 24.9% in 2006 to 31.4% in 2013.[8] Increased utilization of metastasectomy in recent years has not been limited to kidney cancer. Bartlett and colleagues[15] found that metastasectomy increased from 2000 to 2011 across many cancer types, including colorectal, lung, breast, and melanoma. Increase in utilization was greatest in colorectal cancer, which had the most efficacious systemic therapy during the study period.[15]

EVIDENCE FOR METASTASECTOMY IN METASTATIC RENAL CELL CARCINOMA

Multiple reviews and meta-analyses are available to systematically evaluate the evidence for surgery in the treatment of RCC metastases.[16–19] In 2018, Ouzaid and colleagues[16] systematically reviewed the literature and found that median overall survival for patients treated with metastasectomy (36–142 months) was higher compared with patients treated without metastasectomy (8–27 months). Investigating the concept of complete versus incomplete surgical metastasectomy also provides evidence for the possible impact of surgical treatments. Alt and colleagues[14] evaluated 887 patients with multiple RCC metastases from 1976 to 2006, including 125 who had complete surgical metastasectomy. The median cancer-specific and overall survival rates for patients who underwent complete metastasectomy were 4.8 years and 4.0 years, respectively, compared with 1.3 years and 1.3 years, for patients who did not undergo complete metastasectomy. There was a survival benefit provided by complete metastasectomy compared with incomplete metastasectomy when patients had 2 or more metastases.[14] Patients treated surgically, however, had significant differences in disease burden and performance status compared with the nonsurgically treated patients.[14] In a subsequent article from the same institution, evaluating 586 patients with first occurrence of metastases between 2006 and 2017, 158 patients were treated with complete metastasectomy.[20] After adjusting for age, sex, timing, number, and location of metastases, the investigators found that complete metastasectomy was associated with reduced likelihood of death from RCC (hazard ratio 0.47; 95% CI, 0.34–0.65; $P<.001$).[20] Collectively, these data suggest improved survival for patients treated with complete metastasectomy was better than incomplete metastasectomy or no local treatment, although this concept should be investigated in multi-institutional cohorts.

PATIENT SELECTION

Patient selection is critical to achieve optimal outcomes, and metastasectomy for mRCC is one of the best examples of this surgical maxim. Factors associated with improved outcomes after metastasectomy include (1) smaller volume of metastatic disease, (2) slower disease progression, and (3) lack of competing caused for mortality. Prior to metastasectomy, patients should consult with a multidisciplinary team and discuss expectations for outcomes based on individual considerations (**Fig. 1**).

Overall patient health is important to consider prior to surgery (see Fig. 1A). Patients with limited life expectancy because of comorbidities are less likely to benefit from surgery. Although metastasectomy is more likely to be utilized in younger patients,[8] actual patient age may be less important than physiologic age, which is associated with treatment outcomes in older patients with cancer.[21] Performance status is a critical factor associated with survival in mRCC[22] and surgeons should consider patients with better performance status for metastasectomy. It is important, however, to consider how surgery may affect short-term and long-term performance status. Occasionally, performance status may improve for patients with symptomatic metastasis, such as patients with pathologic bone fractures or gross hematuria. Furthermore, because major adverse events of systemic therapies also affect performance status, surgery may improve performance status by delaying systemic therapy and potential adverse events in some patients.

Cancer-specific survival in mRCC patients varies significantly, with many known tumor specific prognostic factors (see Fig. 1B). In general, patients with solitary or low-volume metastatic disease and fewer sites of metastasis have longer expected survival.[23] In addition, patients with initially localized tumors and a longer time from nephrectomy to metastatic diagnosis are more likely to survive longer compared with patients with synchronous metastatic disease.[24] Several validated risk assessment tools estimate overall survival in mRCC[24,25] and may be useful for patients considering metastasectomy.[26] Observed radiographic growth of metastatic tumors also is important as a prognostic factor for survival,[27] and some patients with slow-growing metastases may be observed safely without systemic treatment.[28] Tumor growth despite systemic treatment is associated with poor survival[29] and these patients are unlikely to benefit from aggressive surgery. Rapid progression also is associated with aggressive pathologic features, such as sarcomatoid de-differentiation, and upfront cytoreductive surgery, generally is not recommended.[30] Similarly, Thomas and colleagues[31] found no benefit for metastasectomy after nephrectomy in

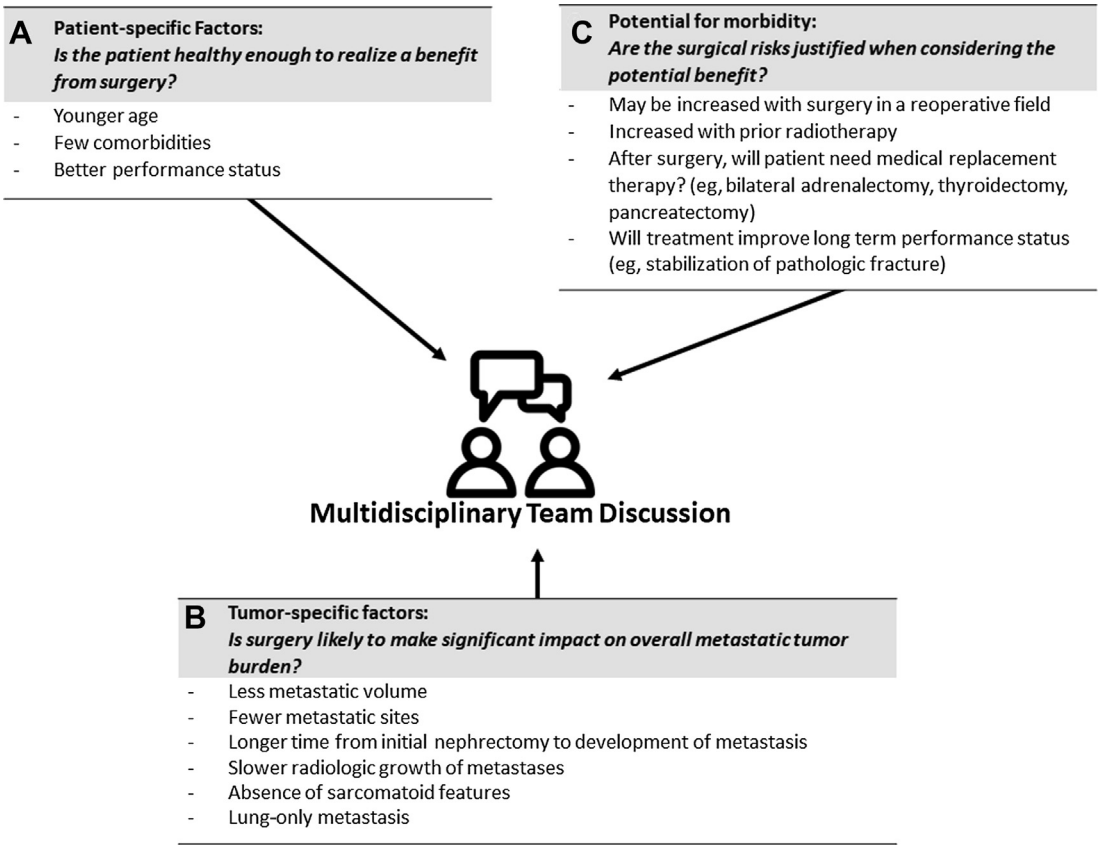

Fig. 1. Prior to metastasectomy, mRCC patients should be counseled by a multidisciplinary team. Using a shared decision-making approach, the treatment team should discuss individual (*A*) patient-specific factors, (*B*) tumor-specific factors, and (*C*) potential for morbidity with surgery or systemic agents.

a matched-pair analysis of mRCC patients with sarcomatoid de-differentiation.

In addition to the patient-specific and tumor-specific factors, shared decision making before metastasectomy should consider the possible short-term and long-term morbidity associated with surgical treatment (see **Fig. 1**C). Morbidity varies with the type of procedure, approach, and anatomic location but may be comparable to other surgeries for primary tumors at those anatomic locations.[16] Surgery may be more complex if scarring is present from prior surgery or tissues are poor quality because of prior radiation therapy. In addition, treatment with targeted therapies for mRCC are associated with wound-healing complications[32] and surgery requires interruption of certain systemic treatments. Other considerations to consider may be the need for medical replacement of hormones after adrenalectomy, thyroidectomy, or pancreatectomy. Informed consent should include a balanced discussion of the risks of surgical as well as the systemic therapies. Given the multiple unique medical and surgical factors to consider before metastasectomy, discussion with a multidisciplinary team of surgeons and medical oncologists is recommended.

INDIVIDUAL METASTATIC SITES

Certain anatomic sites and prognostic factors may be associated with better outcomes in with mRCC metastasectomy sites (**Table 1**). Some anatomic sites are more surgically more accessible, and procedures may be less morbid. For example, patients treated with a minimally invasive wedge resection of a small lung metastasis are exposed to less risk of surgical morbidity compared with an open resection of large liver metastases. More importantly, some metastatic sites are associated with slower disease progression. For example, pancreatic RCC metastatic tumors frequently are

Table 1
Prognostic factors for survival according to anatomic site of metastasectomy

Site	
Lung	• Absence of lymph node involvement[79] • Forced expiratory volume[79] • Longer disease-free interval from initial nephrectomy[79] • Fewer number of metastases[79] • Smaller size of metastases[17] • Unilateral lung involvement[17]
Liver	• Solitary metastasis[17] • No extrahepatic disease[17] • Low tumor grade[17] • No lymph node metastasis at initial diagnosis[42] • Metachronous presentation[42] • Better ECOG performance status[42]
Bone	• Peripheral location of metastases[18] • Solitary metastases[17] • Lower MSKCC risk score[46] • Ability to complete resect tumor[46]
Thyroid	• Solitary metastasis[17] • Younger age[17] • Metachronous presentation • Ability to complete resect tumor
Pancreas	• Asymptomatic presentation[17] • Solitary metastasis[17] • No extrahepatic disease[17] • Absence of vascular invasion[80] • Ability to complete resect tumor
Brain	• No extracranial metastasis[17] • Greater performance status[17] • Solitary metastasis[18] • Age $\leq$65 years old[18] • Control of primary tumor[18]

Data from Refs.[17,18,42,46,79,80]

observed to be slow growing and patients with pancreatic metastasis may have longer survival compared with those with metastasis at other sites.[33] Clinical observations from multiple centers have confirmed these observations and demonstrated that metastasectomy is a feasible treatment in patients with pancreatic RCC metastases.[34] Recently, basic science evidence has emerged that may begin to explain the slower natural history of pancreatic metastasis. In 2018, Turajlic and colleagues[35] observed that pancreatic metastasis had the longest time to presentation of all RCC metastases, which was associated with significantly less chromosomal instability and few additional driver mutations despite longer time to clinical detection.

Pulmonary Metastasectomy

The lungs are the most common site of metastasis for RCC,[36] and pulmonary resections are the most common type of metastasectomy described for mRCC. When investigating survival benefit among anatomic sites of RCC metastasis, a systematic review suggested that pulmonary metastasectomy has the strongest association with a survival benefit.[16] In a meta-analysis of studies evaluating pulmonary metastasectomy for mRCC, poor prognostic factors for survival after pulmonary metastasectomy included multiple pulmonary metastases, incomplete resection, larger size of pulmonary metastasis, lymphatic invasion, and synchronous presentation of metastasis.[19]

Multiple open and video-assisted thoracoscopic surgery (VATS) surgical approaches are used routinely for pulmonary metastasectomy. Expert consensus from the Society of Thoracic Surgeons (STS) recommends using minimally invasive techniques when appropriate for metastasectomy.[37] In general, VATS is used for small solitary unilateral lesions whereas open thoracotomy is used when the lesions are larger and bilateral. In a National Cancer Database population-based cohort, mRCC patients with lung metastasis had significantly better survival at 1 year, 2 years, and 3 years if they were treated with metastasectomy (78%, 59%, and 47%, respectively) versus nonsurgical management (65%, 45%, and 34%).[8] In addition to lung parenchymal metastases, metastatic tumor may be present in the mediastinal lymph nodes or based in the pleura.[38] As such, the STS recommends regional lymph node sampling when clinically suspicious.[37] Long-term survival after mediastinal metastasectomy has been reported[39] but fewer data are available compared with lung parenchymal metastases.

Hepatic Metastasectomy

Liver metastasis is present in approximately 20% of mRCC patients.[36] Historically, liver resection of mRCC lesions was uncommon due to the higher morbidity associated with hepatic surgery.[40] Overall, hepatic metastasis appears associated with poor oncologic outcomes compared with RCC metastasis at other sites.[41] When considering hepatic resection for mRCC, improved overall survival is associated with complete resection, metachronous presentation of metastases, lower primary tumor grade, better Eastern Cooperative Oncology Group (ECOG) status, and lack of extrahepatic metastatic sites.[16] Staehler and colleagues[42] identified 88 patients with liver metastases between 1995 and 2006. A total of 68 patients were treated with liver resection and 20 were managed nonsurgically, serving as a control cohort. The investigators found that metachronous liver metastases treated surgically were associated with significantly better survival compared with the control group, 155 versus 29 months, respectively.[42] The investigators found that hepatic metastasectomy was associated with 5-year survival of 62% but suggest that no benefit is present if metastases are synchronous.[42] In a multi-institutional study of 43 hepatic metastasectomy patients from 1994 to 2011, Hatzaras and colleagues[40] reported a 3-year overall survival rate of 62% and a median length of recurrence-free survival of 15.5 months. No differences in positive margin rates, recurrence, or survival were identified for parenchymal sparing versus anatomic liver resection techniques.[43] Because of the higher risk of morbidity with hepatic surgery, nonsurgical local treatments for liver metastases using radiation or thermal ablation also are common.[18,44]

Bone Metastasectomy

Bone metastases are another common site of RCC metastasis, identified in approximately 30% of mRCC patients,[36] most commonly in the spinal column.[45] One study investigating prognostic factors for mRCC patients with bone metastases found that Memorial Sloan Kettering Cancer Center (MSKCC) risk score, increased number of bone metastases, and radical resection were important prognostic factors for survival.[46] The investigators concluded that surgery with the intention of gaining local tumor control should be considered if a patient presents with solitary bone lesions without concomitant metastases at the initial diagnosis, which may be associated with better overall survival.[46]

When evaluating overall survival, local therapy combined with targeted therapy had superior overall survival benefit compared with local therapy or targeted therapy alone.[47] Median overall survival rate of patients with bone metastases resection (n = 33) was 39.1 months and was significantly longer than those of the patients with resection of any other site (n = 22) and patients without metastasis (n = 59), which were 8.3 months and 7.6 months, respectively.[47] Comparing metastasectomy with no metastasectomy, there was a significant difference between the median overall survival of 17.79 versus 8.71 months.[48] For patients who present with bone metastases who are not surgical candidates, radiation therapy and thermal ablation are local therapy options. A recent systematic review reviewed stereotactic body radiotherapy (SBRT) for mRCC spinal metastases and concluded that there was pain improved in 41% to 95% of patients and that local control rates after stereotactic radiation ranged from 71.2% to 85.7% at 1 year.[49] Toxicity rates ranged from 23% to 38.5%, and there was an increased risk of vertebral compression fracture after treatment.

Pancreatic Metastasectomy

As discussed previously, pancreatic metastases from RCC frequently have been observed to be less aggressive,[33] but morbidity from pancreatic surgery also may be more significant than other anatomic sites. In a series of 97 patients treated with 98 pancreatic metastasectomies from July 1988 through March 2016 for metastatic disease, postoperative complications were reported in 56% patients and perioperative deaths occurred in 3% of patients.[50] Median follow-up was 2.0 years and median survival was 3.2 years. Older patients, non-RCC histology, vascular invasion, and positive resection margins were independently associated with an increased risk of mortality.[50]

A recent systematic review of resection of pancreatic metastasis included 414 pancreatic metastasectomies (techniques included pancreatoduodenectomy 38%, total pancreatectomy 11%, distal pancreatectomy 43%, and enucleation 7%). Overall morbidity and mortality rates were 48.3% and 1.4%, respectively.[51] The investigators concluded that pancreatic metastasectomy was a safe option at experienced centers. Lee and colleagues[50] demonstrated a median survival for 56 patients with resected RCC pancreatic metastases of 4.8 years, which is similar to that in other studies, with 5-year overall survival rates of 48% to 72%.[50–52]

Thyroid Metastasectomy

Although head and neck metastases from mRCC are less common overall, thyroid metastases are well described.[53] In the thyroid gland, metastases usually are single (77%) and unilateral (71%).[53,54] A survival advantage for thyroidectomy has been suggested in isolated singular and multiple metastases.[14,55] The current guidelines of the European Association of Urology recommend metastasectomy in cases of a resectable lesion regardless of the site, whether synchronous or metachronous.[53] No significant survival difference has been shown between total thyroidectomy and subtotal thyroidectomy.[53,56,57] Recurrence in those managed with partial thyroidectomy may be high (20%), which may be related to the presence of positive margins at initial surgery or multifocal disease.[53] Outcomes with thyroid metastases generally are favorable[57,58] with overall 5-year and 10-year survival rates for patients with isolated metachronous thyroid metastasis who underwent metastasectomy being 51.4% and 25.7%, respectively.[56]

Adrenal Gland Metastasectomy

Although the classic description of radical nephrectomy for RCC included ipsilateral adrenalectomy,[59] Weight and colleagues[60] found that ipsilateral adrenalectomy did not lower the risk of subsequent metastasis or improve survival in patients with localized RCC. The 10-year risk for the development of an ipsilateral or contralateral asynchronous adrenal metastasis was equivocal for patients treated with adrenalectomy at the time of nephrectomy.[60] For patients who present with metachronous metastatic tumors in the adrenal gland, minimally invasive surgical techniques may be used,[61] even for adrenalectomy after previous ipsilateral nephrectomy.[62] An open approach may be preferred when periadrenal fat invasion is suspected, when tumor thrombus is present, or for tumors greater than 10 cm.[63] In a study of 1179 patients where 45 had adrenal metastasis, patients with isolated adrenal metastasis survived significantly longer than those with multiple metastasis.[64] Surgical curative outcomes were demonstrated in 10 cases without relapse at a mean follow-up of 82.9 months.[64]

Brain Metastasectomy

RCC metastasis to the brain has a reported incidence of 2% to 17%[65] and multiple reports of curative treatment with complete resection have been published. Historically, brain metastases have been thought to be associated with poor

outcomes, although recent contradictory evidence has suggested that patients with brain metastases may have similar outcomes to other metastatic sites with aggressive treatment.[66] Time to development of metastasis appears to be an important prognostic factor, with brain metastases presenting more than 10 years after the initial RCC diagnosis associated with favorable outcomes.[67] Multiple studies have identified favorable outcomes for some patients with solitary RCC brain metastases after local treatment.[8,66]

MORBIDITY OF TREATMENTS FOR METASTATIC RENAL CELL CARCINOMA

Although systemic therapies have improved survival for mRCC patients greatly, there are significant risks of severe adverse events.[68] Prior to treatment, mRCC patients should discuss the likelihood of adverse events and may consider potential benefits of local treatments. Although many studies have demonstrated low morbidity with surgical metastasectomy,[16] there are conflicting data from population-based studies. Using the National Inpatient Sample database between 2000 and 2011, Meyer and colleagues[69] identified 45,279 patients with mRCC, including 1102 treated with metastasectomy. Overall complications and major complications (Clavien-Dindo III-IV) were identified in 46% and 25%, respectively, of patients, with in-hospital mortality of 2.4%. In a similar study of mRCC treated with metastasectomy from the National Inpatient Sample database between 2006 and 2015, overall complications and in-hospital mortality were 55% and 4.6%, respectively.[70] Potential explanations for the discrepancy in morbidity rates between studies may include the difficulty of accurate recording of complications for rare procedures. Alternatively, higher-volume centers may be more likely to publish data for metastasectomy,[16] which may be skewed because of better outcomes demonstrated at centers with higher volume of mRCC patients.[71] Age, comorbidities, and hepatic surgery are associated with higher risk of major complications.[69]

RADIATION OR PERCUTANEOUS THERMAL ABLATION FOR LOCAL METASTATIC RENAL CELL CARCINOMA TREATMENT

Alternatives to surgical metastasectomy include radiation and thermal ablation. No high-quality data are available to compare outcomes between surgery and other local treatments directly, but there may be potential advantages for some patients and anatomic locations. For example, radiation and thermal ablation may not require general anesthesia and have shorter recovery. Accordingly, the potential benefits of nonsurgical treatments must be balanced with the expected durability of results and goals of therapy in order to select patients appropriately.

Historically, RCC was considered a radioresistant tumor but more recent studies have demonstrated success with SBRT.[72] A recent meta-analysis included 28 studies with 1602 patients and 3892 lesions (1159 extracranial/2733 intracranial).[72] Local control rates were approximately 90% at 1 year and clavien grade III-IV toxicities were identified in approximately 1% of patients. Especially in more frail patients with bone metastases, SBRT may be an effective treatment to decrease pain.[73] Thermal ablation also has been described as a local treatment of mRCC using radiofrequency ablation, cryoablation, or microwave ablation. Percutaneous approaches generally are used with ultrasound or computerized tomography for guidance.

A study by Welch and colleagues[74] evaluated percutaneous image-guided ablations for 61 mRCC patients treated with ablation procedures and found local recurrence-free and overall survival rates at 3 years after ablation were 83% and 76%, respectively. Similarly, Maciolek and colleagues[75] evaluated 18 patients treated with percutaneous microwave ablation for 33 mRCC sites between 2011 and 2016. The ablation locations included the retroperitoneum, contralateral kidney, liver, lung, and adrenal gland. Technical success was achieved for all mRCC tumors and local control was achieved for 28/30 (93%) mRCC tumors, with a median follow-up of 1.6 years. One Clavien grade III complication was identified and the estimated 5-year overall survival was 75%.

COST OF LOCAL VERSUS SYSTEMIC THERAPIES

In addition to delaying adverse events from systemic therapy, it has been suggested that local treatment of mRCC also may be cost effective by delaying or possibly avoiding systemic therapies in a subset of patients.[17] With newer therapies and differences in health care systems direct comparisons are difficult. The annual cost of targeted drug therapies, however, is estimated at $125,000 to $200,000.[76] Furthermore, cost of systemic treatment may increase for additional lines of therapy. In a study that evaluated cost of switching among different treatment mRCC regimens used for first-line, second-line, and third-line mRCC treatments in 767 patients, the investigators found that total costs per patient during the first year increased

from $111,680 for no drug switches; $149,994 for 1 switch; and $196,706 for 2 or more switches.[76] Given that the cost of metastasectomy[77] or thermal ablation[78] is significantly less than systemic therapies in many health care systems, local treatment potentially may decrease overall treatment costs if systemic therapies can be delayed or avoided in some patients.

SUMMARY

The primary rationale for local treatment of mRCC is that metastasectomy may provide systemic treatment-free survival for a subset of patients. Patient selection is critical for optimal outcomes and metastasectomy is less likely to benefit patients who are frail or have aggressive tumor behavior. Utilization of surgical metastasectomy continues to increase despite improved mRCC systemic therapies over the past 2 decades. Future studies will evaluate the optimal role of metastasectomy with newer therapies. Patients considering metastasectomy should receive multidisciplinary evaluation to improved shared decision making.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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