# Metastasectomy in patients with renal cell carcinoma: when and how?

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**Purpose of review**
The role of metastasectomy in the management of metastatic renal cell carcinoma (mRCC) remains controversial. The aim of this review is to summarize and evaluate the recent findings about the surgical treatment of patients with mRCC focusing on the literature published in the last 2 years.

**Recent findings**
Despite the lack of randomized controlled trials, the benefit of metastasectomy in term of cancer-specific and overall survival have been demonstrated in large observational studies. Results of ongoing clinical trials evaluating the impact of combination of surgical and systemic therapies are eagerly awaited and may shed the light on a new treatment armamentarium in this subset of patients.

**Summary**
Several novel systemic agents have emerged and is continuously changing the treatment paradigm in patients with advanced RCC. However, surgical resection of the primary tumor and metastatic deposits represents a definitive cure option in well selected patients.

**Keywords**
metastasectomy, metastatic renal cell carcinoma, renal cell carcinoma metastases, renal cell carcinoma

## INTRODUCTION

Approximately 20–30% of patients with newly diagnosed RCC have synchronous metastatic disease at presentation and, depending on the individual risk factors, up to 40% will subsequently develop metastases after nephrectomy for a localized tumor [1]. The most common sites for metastases in descending order are lung, bone, lymph nodes, brain, liver, and adrenal gland [2]. However, case reports show that metastases of RCC can appear almost in every region of the body [3]. With the better understanding of the genetic and molecular mechanism of RCC tumorgenesis, several novel systemic therapy agents have emerged and providing survival advantages in some patients with advanced disease [4–8]. Surgical resection of the primary tumor and metastatic deposits, namely metastasectomy, remains, however, one of the few options to achieve complete, and possibly durable, cure in selected patients with or without systemic therapies.

## EVIDENCE ACQUISITION

A PubMed/MEDLINE search of English-language literature published between January 2017 and January 2019 was conducted using following terms in isolation or combination: 'Renal Cell Carcinoma', metastatic RCC' 'RCC', 'Metastasectomy'. Relevant articles were retrieved after title and abstract screening. We considered original articles that evaluated patients with mRCC treated with surgical resection of metastatic deposits with or without systemic therapies.

### Complete versus incomplete or no metastasectomy

According to the current European Association of Urology (EAU) guidelines, metastasectomy is recommended for patients in whom complete surgical resection is technically feasible or for local control of symptoms [9]. These recommendations are based on data from eight studies assessing oncologic

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## KEY POINTS

- Although novel systemic therapy agents have shown considerable survival advantages in patients with mRCC, metastasectomy of RCC metastases remains to play an essential role in the management of selected patients with mRCC.
- Metastasectomy appears to offer survival advantages, extend time to initiation of systemic treatment, and provide local symptom control.
- Patients with long-disease free interval between primary RCC resection and metastasectomy, good performance status, and in whom complete resection of all metastatic sites is technically feasible appear to benefit most from metastasectomy.
- Results from ongoing clinical trials focusing on the combination of systemic therapy and metastasectomy will shed the light on the optimal treatment regimen in patients with mRCC.

outcomes of local treatment of metastatic spots from RCC in various organs comparing complete versus incomplete/no metastasectomy. The majority of the studies favored complete metastasectomy, with significantly longer survival rates [median of medians (OS or CSS) 40.8 vs. 14.8 months, IQR = 31.6–48.0 months) compared with incomplete or no metastasectomy [10]. However, all included studies were nonrandomized comparative observational studies with its well known limitations such as selection bias limiting the quality of such data.

A recent systematic review and meta-analysis [11] identified eight retrospective studies including more than 2200 patients with 42.3% underwent complete metastasectomy compared to 57.7% with no/incomplete metastatectomy. The median OS ranged between 36.5 and 142; and 8.4 and 27 months for complete metastasectomy and no/incomplete metastasectomy, respectively. Additionally, complete metastasectomy was associated with a reduced risk of all-cause mortality compared with incomplete metastasectomy (HR = 2.37; 95% CI, 2.03–2.87).

Despite the fact that there are no randomized controlled trials on this topic to date, data from these observational studies support the beneficial effect of complete metastasectomy on survival outcomes.

### Combination of surgical and systemic therapy

Systemic therapy for mRCC has witnessed dynamic changes over the past decades with novel agents showing considerable advantages and thus gaining approval in this subset of patients. Theoretically, combination treatment might offer potential superior outcomes optimizing patients care, quality of life, and potentially improving survival. However, the optimal regimen, sequence, and timing for medical treatment and surgical intervention have not been defined yet [12▪▪].

After resection of the primary tumor and complete metastasectomy, patients are referred to as having no evidence of disease. These patients represent a unique cohort because their tumor has already demonstrated the ability to spread to distant sites and they are at risk of recurrence highlighting the importance of addressing tumor biology in treating this subset of patients. Appleman *et al.* [12▪▪] reviewed ongoing clinical trials addressing the role of systematic therapy in the adjuvant setting after metastasectomy. The presented studies are enrolling patients who have undergone metastasectomy and randomizing them to systemic agents versus placebo. The authors from the review concluded that the results from these ongoing clinical trials may change postoperative systemic therapy in patients with mRCC after metastasectomy. However, because results from these studies are still pending, observation remains the standard of care for patients with no evidence of disease after surgical resection of all metastatic deposits.

A recently published retrospective study compared survival outcomes of patients with mRCC who had received targeted therapy only versus targeted therapy and complete metastasectomy versus targeted therapy in combination with incomplete metastasectomy. Median OS was 2.4, 5.05, and 3.5 years for the targeted therapy-only group, the complete resection group, and the incomplete resection group, respectively ($P = 0.024$). The authors concluded that this significant survival benefit of combined therapy could permit drug holidays, hence periods without systemic treatment and drug-related toxicity in addition to potential complete cure. However, this study was limited by the retrospective design, and the small patient number ($n = 124$). In addition, the targeted therapy-only cohort had a significantly higher percentage of Memorial Sloan Kettering Cancer Center (MSKCC) poor-risk patients compared with the complete resection and incomplete resection group (22.7 vs. 3.8 and 0%, $P = 0.006$). The favorable features of patients who underwent complete metastasectomy may have influenced the results and be the cause of better survival outcomes [13].

A prospective phase I/II study (NCT02429440) on the efficacy, safety, and tolerability of an adjuvant multipeptide vaccine (UroRCC) after metastasectomy

has shown promising initial results [14]. Nineteen patients with mRCC received UroRCC after metastasectomy and their outcomes were compared with a retrospectively evaluated contemporary cohort of 44 patients, who had undergone metastasectomy without adjuvant therapy. In general, the vaccination was well tolerated with side effects mainly limited to the injection site (i.e. local inflammation reactions). Median OS for the UroRCC group was not reached (mean = 112.6 months; 95% CI, 92.1–133.1) compared with 57.96 months (95% CI, 37.2–63.1) in the control group ($P = 0.015$). Immune response was induced in the majority of patients and UroRCC-treatment after metastasectomy remained an independent prognostic factor for OS in multivariable analysis adjusted for MSKCC risk-group, metastatic site, and age (HR = 0.19; 95% CI, 0.05–0.69). Further studies to validate these findings on larger phase III trials are needed to consider this therapy as an adjuvant post-metastasectomy treatment option.

## METASTATIC SITES

### Lung

The lung represents the most common site of metastases in patients with RCC [2]. The first reported metastasectomy of a single pulmonary deposit in a patient with RCC was reported in 1939 by Barney and Churchill, with patient survival for over 2 decades without evidence of recurrence [15]. Because no randomized trial is available on lung-specific metastasectomy, the evidence is of limited quality based mainly on retrospective data and case reports.

Murthy *et al.* evaluated 417 patients with lung metastases from RCC, of whom 92 had undergone metastasectomy. They identified incomplete resection as the strongest risk factor for time-related mortality with a 5-year survival of 8% for incomplete and 45% for complete resection. Other risk factors included larger size of nodules ($P = 0.0001$) and increasing number of involved lymph nodes ($P = 0.01$). In those patients with complete resection, a shorter disease-free interval (DFI) was a risk factor ($P = 0.01$) for death [16]. A retrospective evaluation of 84 patients revealed clear cell histology (HR = 0.37; 95% CI, 0.16–0.83) as a favorable prognostic factor in multivariate analysis, alongside tumor size less than 2 cm (HR = 0.31; 95% CI, 0.13–0.78) and complete resection (HR = 0.27; 95% CI, 0.10–0.78; $P = 0.015$) [17].

In a large systematic review and meta-analysis including sixteen studies with a total of 1447 patients with mRCC, Zhao *et al.* identified the following factors as predictors of poor prognosis after lung metastasectomy: lymph node involvement of primary RCC (HR = 3.44; 95% CI, 1.78–6.67), incomplete of resection of metastatic deposits (HR = 3.74; 95% CI, 2.49–5.61), multiple metastases (HR = 1.55; 95% CI, 1.18–2.03), larger size of metastases (HR = 1.45; 95% CI, 1.26–1.66), lymph node involvement of metastases (HR = 3.06; 95% CI, 1.52–6.19), synchronous metastasis (HR = 2.49; 95% CI, 1.46–4.24), and short DFI [18].

The therapeutic approaches for the treatment of lung metastases have evolved during the past decades with novel modalities such as laser resection under video-assisted thoracoscopy presenting a well tolerated and minimally invasive technique, especially in comorbid patients. In their pilot study, Meyer *et al.* [19] demonstrated the effectiveness of this new approach on pulmonary metastases from different primary tumors including two cases with primary RCC. Such minimally invasive interventions are expected to increase the number of patients who are eligible of metastatic sites resection potentially benefitting improving the outcome of patients and improving the quality of the current evidence on the exact role of metastasectomy in RCC patients.

In conclusion, contemporary data consistently point toward a beneficial role of lung metastasectomy in patients with resectable metastatic deposits based on the reported 5-year survival rates which were ranging from 43 to 75% [17,18,20].

### Bone

The second most common site of metastases is the skeletal system with incidence rate ranging from 15 to 23%. The presence of osseous metastases is generally associated with poor prognosis. However, the reported 5-year survival rate in patients after metastasectomy for a solitary bone metastasis was 35% [21,22].

Higuchi *et al.* [23] reported more favorable survival rates with a 5-year survival of 62% in patients with resection of bone or soft-tissue metastases from RCC. Possible reasons for the advanced survival could be that all patients in this study underwent nephrectomy and the majority of patients received either cytokine-based therapy or targeted therapy or both, which has already been shown to improve prognosis [24]. Furthermore, it was a single-center study, so the treatment strategy of metastases of this specific hospital may have influenced the results. Nonclear cell histology and metastases to more than two sites have been shown to be independent risk factors for poor prognosis [23].

The same group retrospectively compared outcomes of patients with bone or soft tissue metastases who had undergone wide resection to those who

had been treated with intralesional resection. Survival rates were significantly more favorable in the wide resection group and intralesional resection was an independent risk factor for poor prognosis in multivariate analysis [25].

### Retroperitoneum

Retroperitoneal sites of metastases include lymph nodes, soft tissue, psoas muscle, and adrenal gland with an incidence rate of approximately 3% in patients with mRCC [21].

The current EAU guidelines recommend extended lymph node dissection (LND) only in patients with adverse clinical features (e.g. advanced diameter of the primary tumor or presence of sarcomatoid features) [9]. Only one prospective randomized clinical trial (RCT) has assessed the clinical value of LND in combination with radical nephrectomy for primary RCC with no evidence of clinical lymph node involvement or distant metastases. The incidence of lymph node metastases was low and no survival advantage was demonstrated in the complete LND arm [26]. In contrast, in cases of evident lymph node involvement, the goal is to resect the enlarged lymph nodes with curative intent. Recently, the role of retroperitoneal LND was assessed in a literature review [27▪].

In a large population-based study including more than 9500 patients who had undergone nephrectomy with LND, Whitson *et al.* [28] observed an increased disease-specific survival (DSS) with greater extent of LND. However, a survival benefit was only demonstrated in patients with positive lymph nodes, whereas patients with no evidence of lymph node involvement did not experience DSS advantage after extended LND.

Delacroix *et al.* identified single node involvement as a predictor of favorable outcome on multivariate analysis, alongside an Eastern Cooperative Oncology performance status of 0, absence of sarcomatoid features and papillary histology. The authors concluded that in patients with regionally advanced disease with limited lymph node involvement, LND would provide a durable disease-free survival [29].

Based on their findings, the authors suggested that retroperitoneal LND may be beneficial in patients with locally advanced or oligometastatic disease [27▪].

### Liver

Metastasis to the liver is reported with an incidence of approximately 20% [21]. Data from retrospective studies showed survival benefit from surgical resection of liver metastasis if technically feasible with 5-year survival rates ranging from 38.9 to 62.2% [30–33].

In univariate analysis, Thelen *et al.* identified resection margin ($P = 0.008$), DFI ($P = 0.012$), and primary tumor site (right kidney vs. left kidney; $P = 0.013$) as prognostic factors for survival. However, in multivariate analysis, only resection margin remained statistically significant ($P = 0.005$) [33]. Again, these findings emphasize the impact of complete resection of all metastatic deposits on survival outcomes of patients with mRCC.

### Brain

Outcomes in patients with brain metastasis are worse compared to other metastatic sites, with a 5-year survival of 12% and median survival time of 4–11 months [21]. Recommendations in the EAU guidelines favor stereotactic radiotherapy (SRT) for local control or symptom relief for clinically relevant bone metastases based on two comparative studies [9].

A retrospective study compared SRT alone versus SRT plus whole brain radiotherapy (WBRT) versus WBRT alone in patients with brain metastases from RCC. No statistical differences regarding OS were found between SRT and SRT plus WBRT (12 vs. 16 months, respectively) emphasizing the potential of SRT in the treatment of brain metastases [34].

Ikushima *et al.* assessed survival and local control rates for patients with brain metastases who had been treated with fractionated SRT (FSRT) versus surgery followed by conventional radiotherapy (CRT) versus CRT alone. Survival and tumor control were superior in the FSRT group. In multivariate analysis, prognostic factors associated with survival were a good performance status ($P = 0.06$), age less than 60 years ($P = 0.003$), and treatment of metastases by FSRT ($P = 0.04$) [35].

## PANCREAS AND THYROID

RCC metastases to pancreas and thyroid are rare, occurring in 1% or less of patients. Metastases to these infrequent sites are mostly described in case reports with a small number of available cohort studies in current literature.

In a recent retrospective study, pancreatic metastases from different primary tumors were evaluated in 98 patients treated with surgical resection. Of those patients, 57 had primary RCC. In multivariate analysis, non-RCCs were independently associated with an increased risk of mortality (HR = 5.07; $P < 0.001$), indicating the favorable long-term outcomes for

**Table 1.** Factors associated with poor prognosis based on organ/site in patients with metastatic renal cell carcinoma [16–18,21–23,25,26,28–33,35,36,39]

| Organ/site | Included studies | Incidence in mRCC | 5-year OS | Factors associated with poor prognosis |
|---|---|---|---|---|
| Lung | [16–18] | 45–75% | 43–75% | Incomplete resection<br>Larger size of metastases<br>Lymph node involvement of primary RCC and metastases<br>Short DFI<br>Synchronous metastasis |
| Bone | [21–23,25] | 15–23% | 35–62% | Nonclear cell histology<br>Metastases to more than 2 sites<br>Intralesional resection |
| Liver | [30–33] | 20% | 38.9–62.2% | Positive resection margins<br>DFI <24 months<br>Poorly differentiated metastases |
| Retroperitoneum | [26,28,29] | 3% | 35% | Sarcomatoid, collecting duct and medullary histology<br>Higher pN stage at original nephrectomy<br>larger diameter lesion |
| Brain | [35] | 17% | 12% | Age ≥60 years<br>More than 1 lesion<br>Treatment other than FSRT |
| Pancreas | [36,39] | ≤ 1% | 57–88% | Non-RCC histology |
| Thyroid | [21] | ≤ 1% | 51% | Age >70 years<br>Metastatic disease to the contralateral kidney |

DFI, Disease-free interval; FSRT, fractionated stereotactic radiotherapy; RCC, renal cell carcinoma.

metastasectomy for pancreatic RCC metastases [36]. Findings regarding 5-year survival rates from previous studies range between 57 and 88% and emphasize the survival benefit of pancreatic metastasectomy [37–39].

## PROGNOSTIC FACTORS AND PATIENT SELECTION

Because aggressive surgical resection of metastasis appears to improve survival outcomes, patient selection plays a fundamental role in providing the optimal treatment improving quality of life and possibly survival outcome.

Several predictors of poor prognosis have been identified such as short DFI, multiple and larger metastases, lymph node invasion of both primary RCC, and metastases and synchronous metastasis [10,18]. Such data are not only important for patient selection regarding treatment planning, but also for designing future studies.

Verbiest *et al.* have identified four molecular subtypes of clear cell RCC (ccRCC1–4) and evaluated their impact after metastasectomy. The intermediate/poor-prognosis ccRCC1&4-tumors were significantly at higher risk of relapse and the good-prognosis ccRCC2&3-subtypes experienced longer disease-free survival. The authors concluded that these molecular subtypes could have an impact on patient-selection, because they were associated with an increased probability to predict which patients were at higher risk for early recurrence after surgical metastasectomy and therefore would benefit from alternative treatment options. However, the results should be further validated in larger cohort studies before implementation as prognostic markers [40▪].

### Complications related to metastasectomy

In a large population-based study, Meyer *et al.* [41] identified 45 279 patients with mRCC diagnosed between 2000 and 2011 using the National Inpatient Sample database. Of those patients, 1102 had undergone metastasectomy. The overall complication rate was 45.7% with blood transfusion (13.5%) and respiratory complications (12.0%) being observed the most common adverse events. Intraoperative complications and major complications (Clavien III–IV) were found in 7.9 and 25.1% of patients, respectively with in-hospital mortality rate of 2.4%. On univariate analysis, advanced age, hepatic and pulmonary metastasis (both compared with any other site) as predictors of overall complications, whereas major complications were associated with a high comorbidity burden. However, a clear definition of important patient features such as prior oncologic interventions, numbers, and size of the resected metastases at the time of surgery and complete/incomplete metastasectomy in curative or

palliative intention was not provided. Further, the results showed only in-hospital events, hence long-term complications after discharge were not assessed and could lead to an underestimation of overall complications after metastasectomy.

In a matched-cohort study, 34 patients underwent aggressive surgical management in the form of nephrectomy with simultaneous hepatic resection for advanced or mRCC. Perioperative outcomes and complication rates were compared with a matched cohort of 68 patients undergoing nephrectomy with simultaneous metastasectomy or en-bloc resection of neighboring nonhepatic organs (i.e. adrenal gland, muscle, bowel, and pancreas). Complete metastasectomy was reported in 82% of hepatic resection cohort and in 90% of the referent cohort. Despite a more frequently observed incidence of postoperative deep vein thrombosis following hepatic resection, no significant differences were detected in Clavien III–IV complications or perioperative mortality. The authors suggested that in selected patients, aggressive surgical intervention should be considered because simultaneous hepatic resection at the time of nephrectomy was not associated with significantly higher rates of major complications compared with the referent cohort [42].

These studies provide data on the rate of complications after surgical resection of metastases in patients with mRCC, a topic that has not been addressed frequently in the literature to date. Further research is needed to improve the level of evidence in this field to guide clinicians in decision-making and patient counseling.

## Ablative therapies in the treatment of metastases from RCC

Historically, RCC has been considered refractory to conventional radiation therapy (RT) [43,44]. Therefore, metastases from RCC have been mainly treated with RT for local symptom control and pain relief with a palliative intent with variable response rates [45].

Stereotactic body radiation therapy (SBRT), however, has gained acceptance in treating primary and oligometastatic RCC. SBRT involves the delivery of 1 or a few ablative high-dose fractions (typically $\geq$8 Gy per fraction) to tumors with minimized doses to surrounding organs [46].

While the role of SBRT and radiosurgery (SRS) in the management of brain metastases in patients with RCC is well established, interest in the use of SBRT as a treatment alternative for extracranial metastases is increasing [47].

In a systematic review and meta-analysis [48] including 810 patients with intracranial and 389 patients with extracranial metastases from RCC treated with SBRT, Kothari *et al.* revealed a weighted local control rate of 92% for intracranial and 89% for extracranial metastases, respectively. Regarding the incidence of grade 3–4 toxicities, the reported rates ranged from 0 to 6% and 0 to 4% in patients with intracranial metastases and those with extracranial metastases, respectively.

In a recently published retrospective study, Franzese *et al.* [49] reported on the outcomes of 58 patients who had received SBRT for the treatment of metastases of RCC. The authors reported a local control rate of 90.2 and 90.2% at 12 and 18 months, respectively. Progression-free survival at 12 and 18 months was 46.2% (95% CI, 32.2–59.0) and 35% (95% CI, 21.4–48.9), respectively. Metachronous and single metastases were associated with improved progression-free survival both in univariate and multivariate analysis.

Another study compared the impact of SBRT, surgical metastasectomy or both modalities sequentially on survival outcomes in patients with mRCC. Median overall survival for all patients was 51 months after a median follow-up time of 63 months (range = 22–142) and there was no significant difference between SBRT, surgical metastasectomy, or the combination of both modalities. Independent prognostic factors of overall survival were intracranial targets (HR = 1.8; 95% CI, 1.1–3.2), ECOG performance score 1 versus 0 (HR = 2.9; 95% CI, 1.6–5.2) and watchful waiting more than 18 months before treatment (HR = 0.3; 95% CI, 0.2–0.6) [50].

Data from several studies investigating the outcomes in patients receiving a combination of ablative radiotherapy and targeted therapy show promising results [13,51,52].

Staehler *et al.* [53] evaluated 106 patients with spinal or cerebral metastases from RCC who had received either sorafenib or sunitinib and simultaneous SRS. Overall survival was 17.4 months in patients with spinal metastases and 11.1 months in patients with cerebral lesion ($P = 0.038$), respectively. The authors did not observe any adverse effects caused by SRS and typical adverse effects of the targeted agents were not altered by SRS.

In a retrospective study, Miller *et al.* [52] reported on 100 patients with spinal metastases from RCC, receiving SRS alone, SRS with concurrent systemic therapy with tyrosine kinase inhibitors (TKIs) or SRS after initial TKI-therapy. On multivariate analysis, concurrent TKI and SRS therapy was associated with a local control benefit (HR 0.21, $P = 0.04$), whereas the local failure rate under TKI treatment alone was increased (HR 2.43, $P = 0.03$). No grade 3–4 toxicities were observed during SRS and simultaneous TKI therapy.

The use of SBRT in treating patients with RCC has increased owing to the recent technological advances that allowed a safe delivery of high-dose ablative fractions. Combinations of ablative radiotherapy with systemic targeted treatment might improve outcomes.

Also, evidence is accumulating that radiotherapy has an immune-stimulating effect augmenting antitumor immune response [54].

Several prospective studies investigating the effects of concomitant SBRT and immunotherapy are underway and will bring further information on the safety and potential benefit of combined therapy (NCT02855203, NCT02864615, NCT01896271, NCT02599779).

## CONCLUSION

Metastasectomy is a major part in the treatment landscape of mRCC. Complete resection of the primary tumor and all metastatic deposits appears to play an important role in achieving complete and durable cure. Additionally, metastasectomy significantly prolongs survival, extends time to systemic treatment, and represents an effective palliative therapy option for the control of tumor-related symptoms. Advances in technology have provided the safe delivery of ablative doses of radiotherapy with good local tumor control rates leading to an increased used of this treatment option in the clinical management of patients with mRCC.

The results of ongoing clinical trials will provide further information regarding the benefits of combined surgical or ablative and systemic therapy and their role in the definite treatment of patients with mRCC.

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*There are no conflicts of interest.*

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- ■ of special interest
- ■■ of outstanding interest

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