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ORIGINAL ARTICLE

# Surgical metastasectomy for metastatic renal cell carcinoma in the era of targeted and immune therapy: a narrative review

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## Abstract

**Purpose** Metastatic renal cell carcinoma (mRCC) still harbours a big propensity for future metastasis. Combinations of immune and targeted therapies are currently the cornerstone of management with a less clear role for surgical metastasectomy (SM).

**Methods** We performed a narrative review of literature searching for the available evidence on the yield of surgical metastasectomy in the era of targeted and immune therapies. The review consisted of a PubMed search of relevant articles using the Mesh terms:" renal cell carcinoma", "surgery», «resection", "metastasectomy", "molecular targeted therapies", "immune checkpoint inhibitors" alone or in combination.

**Results** In this review, we exposed the place of surgical metastasectomy within a multimodal treatment algorithm for mRCC Also, we detailed the patient selection criteria that yielded the best results when SM was performed. Finally, we discussed the feasibility and advantages of SM per organ site.

**Conclusion** Our work was able to show that SM could be proposed as a consolidation treatment to excise residual lesions that were deemed unresectable prior to a combination of systemic therapies. Contrastingly, it can be proposed as an upfront treatment, leaving systemic therapies as an alternative in case of future relapse. However, patient selection regarding their performance status, metastatic sites, number of lesions and tumorous characteristics is of paramount importance.

**Keywords** Renal cell carcinoma · Surgery · Resection · Metastasectomy · Molecular targeted therapies · Immune checkpoint inhibitors

## Introduction

Renal cell carcinoma is a neoplasm with a high propensity for future metastases [1]. The treatment of metastatic renal cell carcinoma (mRCC) was first carried out through cytokine therapy which allowed only modest survival and remission outcomes when compared to targeted therapies, namely tyrosine kinase inhibitors (TKIs): sunitinib [2], sorafenib [3], and pazopanib [4]; the vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab

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in combination with interferon-alpha [5], the mechanistic target of rapamycin inhibitors temsirolimus [6], everolimus [7] and immune checkpoint blockers (ICI) [8].

Metastasectomy for oligometastatic RCC remains a standard of care to achieve complete remission [9]. However, the keynote-564 trial with a small population of metastatic patients with no evidence of disease (M1 NED), there are currently no prospective randomised trials comparing up front metastasectomy to multimodal treatment with initial systemic therapies (ST) and surgery of residual masses.

The aim of this study was to review the available evidence from the medical literature on the different surgical strategies to manage oligo-metastatic RCC in the era of targeted therapies and ICI.

## Methods

We performed a narrative review of literature regarding the surgical resection of metastases in the era of targeted therapies and ICI, through a PubMed search using the following Mesh terms: "renal cell carcinoma", "surgery", "resection", "metastasectomy", "molecular targeted therapies", "immune checkpoint inhibitors" alone or in combination. The literature search was conducted without a time limit till October 2022. We mainly selected articles comparing targeted therapies to surgery in mRCC, as a monotherapy, and those discussing surgical metastasectomy in the context of a multimodal approach. We also selected articles providing evidence concerning the selection of candidates for surgical metastasectomy, regarding patient characteristics, pathological and morphological characteristics of the primary tumour or the metastases including metastatic sites. A few articles discussing the outcomes of surgical metastasectomy according to specific localizations have also been considered. Sources treating other methods of local control of metastases and case reports were not considered for reporting. Article selection was based on abstract initial review by the authors, GAT and AI, selecting only articles in English language. The analysis of evidence was made through a narrative descriptive approach. Article selection was performed according to The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Fig. 1).

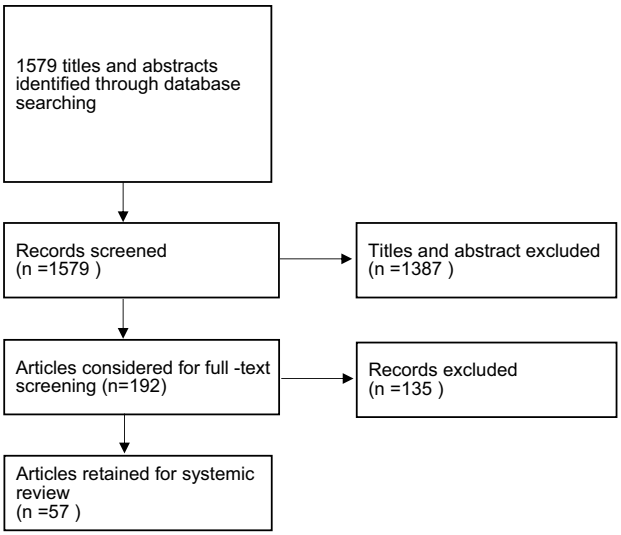


**Fig. 1** PRISMA flow chart

### Landscape of the systemic therapy of mRCC using targeted therapies

The treatment of mRCC improved over the years with the introduction of TKI and ICI mainly used in combination protocols, as stratified by the International Metastatic RCC Database Consortium (IMDC) risk groups [10]. This approach allows also a succession of treatments in the eventuality of failure of an already ongoing protocol. Overall, the treatment combinations that are currently proposed mainly consist of: nivolumab–ipilimumab, pembrolizumab–axitinib [11], pembrolizumab–lenvatinib [12], and nivolumab–cabozantinib. The observed effect, following an initial risk stratification, was a prolonged progression-free survival (PFS) when compared to the effectiveness of the standard treatment with sunitinib that was used as a comparator. Also, these combinations conferred an additional overall survival (OS) advantage [13], without affecting the patient quality of life (Qol). Until recently, the interest in surgery for the treatment of mRCC in the era of systemic therapies (ST) mainly concerned the cytoreductive approach with an ongoing debate over the use of ST in a deferred or upfront strategy.

Conversely, only few articles discussed the role of surgery of metastasis in the era of targeted and ICI therapies,with most studies being of very low evidence and scattered over the years [14–16].

### The yield of SM monotherapy

Surgical metastasectomy (SM) can be defined as the complete or incomplete surgical removal of secondary lesions [17].

According to a systematic review by Zaid et al., complete metastasectomy in patients with mRCC decreased overall mortality [18]. However, mRCC patients are a heterogeneous population when it comes to the number of metastases, their sites, the time interval between localised and metastatic RCC, the primary tumour stage and patient characteristics. Whilst some studies advocated for complete tumour resection in patients with solitary or multiple metastases [18], others suggested that the best candidates for surgical metastasectomy are those with solitary or oligometastatic lesions

[19]. Other selection criteria included patients with symptomatic metastases, those with resistance to radiotherapy or targeted therapies, those with lesions that are surgically accessible, and those with slower disease progression [19, 20]. As mentioned before, response to surgical metastasectomy seems to be dependent on the metastatic site. For instance, patients with pulmonary metastases, who achieved complete resection responded well after surgery. However, incomplete resection, mediastinal nodal involvement and multiple metastases were associated with poor prognosis [21, 22]. Other sites, namely bone and brain metastases, are less accessible than pulmonary lesions, leading to worse oncologic results and more complications. In these cases, surgery is mainly palliative, aiming to decrease pain or restore neurological function [23].

The majority of the overall pancreatic metastases (69%) have the particularity to follow a somehow more indolent course with a median survival of around 19 months after diagnosis[24, 25], and their CR yielded a prolonged OS when compared to conservative therapeutic options, with a relatively low mortality, but nonetheless considerable morbidity, sometimes reaching 50% of cases [24].

On the other hand, a good performance status (PS) was fundamental for patients with liver and/or pancreatic lesions in order to achieve survival benefits from surgical metastasectomy, whilst some authors demonstrated an increase in OS in patients achieving complete resection through metastasectomy [26], regardless of their PS [18].

In the absence of well-established guidelines concerning surgical metastasectomy, patient selection remains crucial in order to ensure both patient safety and disease control. In addition, surgical complete resection, when feasible, is a key point to eradicate visible disease and decrease mortality.

### *The multimodal approach (***Table 1***)*

The concept of multimodal therapy for mRCC is currently the cornerstone of modern studies that find their rationale in the increased effectiveness of targeted therapies, which made possible at times, the CR of all macroscopic disease. In other words, it is the combination of ST with a local control of primary/secondary tumorous lesions.

In a multicentric retrospective study evaluating 64 mRCC patients treated by sorafenib or sunitinib, it was found that CR was obtained using TKIs alone in 36 patients after a median time of 12.6 months (range, 2–28 months), whilst another 28 patients achieved the same oncologic result after a complementary local treatment (79% of the latter underwent surgical metastasectomy) following a median time of 18.5 months (range, 5–45 months) of TKI treatment [27–29]. According to this study, local treatment of metastases, including surgery, can be proposed as a second-line treatment to achieve complete remission after a prolonged treatment with TKIs. However, there wasn't any reliable conclusion concerning the continuation or withdrawal of TKIs after complete remission has been achieved. Upon stratification according to prognostic risk criteria, the study results suggested that patients achieving complete remission with TKI monotherapy or combined with local treatment were in majority of good or intermediate prognostic risk [27].

There is now a solid bulk of evidence to support the fact that the complete resection of metastases improved survival in mRCC when compared to no or incomplete resections [18, 21, 30, 31]. The first meta-analysis conducted by Zaid et al., included 2267 patients with mRCC from 8 comparative studies, who underwent either complete or incomplete resection of metastatic lesions. The majority of patients had RCC or RCC component histology. The OS, which was the primary outcome of this meta-analysis, differed significantly between both groups. In fact, patients with complete surgical resection had an OS between 36.5 and 142 months, whilst that of patients failing to achieve complete resection status ranged between 8.4 and 27 months ($p < 0.001$) [18]. Similar results were reported by the comparative study of Dabestani et al., which found a significantly longer cancer-specific survival (CSS) in patients undergoing complete vs incomplete resection (40.8 vs 14.8 months) with however a higher risk of bias [30].

In a retrospective comparative study conducted by Alt et al., the 5-year CSS was evaluated in 125 patients who underwent CR and 762 patients with mRCC who did not undergo surgical metastasectomy. The authors reported a prolonged CSS in favour of surgical metastasectomy (4.8 vs 1.3 years, $p < 0.001$). Furthermore, complete resection improved survival in patients with 3 or more metastasis ($p < 0.001$), and patients with synchronous ($p < 0.001$) or asynchronous ($p = 0.002$) multiple metastasis [21].

The same conclusion could be drawn from the review of *Zaid* et al. concluding that failure to achieve a complete resection status was predictive of an increased overall mortality with a HR of 2.37 (95% CI 2.03, 2.87; $p < 0.001$). In a review of studies investigating patients with mRCC to single or multiple organs [18], it was found that most studies included patients who had already received ST at some point, hence labelling them as having had a multimodal approach. Even though most studies included patients with multiple metastatic sites, the review still managed to demonstrate that patients with a complete resection of metastases had a better survival when compared to patients who failed to achieve such a status. In fact, the latter had an increased adjusted overall mortality with a HR of 2.37 (95% CI 2.03, 2.87; $P < 0.001$), and low heterogeneity ($I2 = 0\%$). The review also suggested that the optimal strategy for relapsing patients after surgery was to administer ST, as by the National Comprehensive Cancer Network (NCCN) guidelines [18, 32].

**Table 1** Summary of data discussing SM within the multimodal approach for mRCC

| Study | Design | Year | N | Major outcomes | References |
|---|---|---|---|---|---|
| Albiges | RSS | 2012 | 64 | CR status can be obtained with TKI monotherapy<br>SM can be used in second-line after a prolonged course of TKI monotherapy<br>Patients achieving CR with TKI monotherapy or combined with local treatment were in majority of good or intermediate prognostic risk | [36] |
| Staehler | RSS | 2010 | 88 | The five-year OS survival rate after liver metastasectomy was 62.2% ± 11.4% (SEM) with a MS of 142(95% CI 115–169) months vs 29.3% ± 22.0% (SEM) with a MS of 27 (95% CI 16–38) months ($P = 0.003$) in patients who declined surgery<br>79% of patients were receiving TKIs | [40] |
| Zaid | Review of prospective cohort studies | 2016 | 2267 | Complete surgical metastasectomy was a protective factor against all- cause mortality when compared to incomplete excision of metastases (pooled aHR 2.37, 95% CI 2.03–2.87, $p < 0.001$), and that is regardless of performance status<br>The best outcomes for CM were for single metastatic sites with even enhanced survival benefits for pulmonary metastases | [25] |
| Dabestani | Systematic review of literature and meta-analysis | 2014 | 2350 | Patients achieving a metastases-free status following surgery have better survival and symptom outcomes than patients receiving conservative measures only | [39] |
| Thierry-Villeumin | Retrospective multicentric study | 2017 | 224 patients with mRCC undergoing first-line systemic therapy | Surgical metastasectomy was a favourable prognostic factor in patients undergoing systemic first-line therapy HR = 0.667(0.468–0.951) | [42] |

**Table 1** (continued)

| Study | Design | Year | N | Major outcomes | References |
|---|---|---|---|---|---|
| You | Prospective cohort study | 2016 | 325 patients | The median PFS of patients undergoing complete, incomplete or no metastasectomy groups was 29.5 (95% CI 17.3–41.7 months)), 18.8(95% CI 11.7–25.9 months) and 14.8 months (95% CI 12.0–17.6 months respectively ($p < 0.001$)<br>The median OS in the complete, incomplete and no metastasectomy groups was 92.5 months (95% CI 62.6– 122.4 months), 29.6 months (95% CI 15.4–43.8 months) and 23.5 months (95% CI 18.9– 28.1 months) respectively ($p < 0.001$)<br>TKI provided significantly better PFS and OS than TKIs | [43] |
| Choueiri | double-blind, phase 3 trial | 2021 | 496 patients | Pembrolizumab treatment significantly improved disease-free survival as compared with placebo after nephrectomy in both M0 and M1 NED patients | [48] |
| Alt | Retrospective case control study | 2011 | 887 patients | CR patients had a CSS and OS of 4.8 and 4 years respectively whereas patients who did not achieve a CR status only achieved 1.3 years in terms of both CSS and OS ($p < 0.001$ for OS and CSS)<br>The initiation of systemic therapies improved CSS only in the latter group from 1.1 to 1.6 years ($p = 0.01$) | [28] |
| Dragomir | Cohort study | 2020 | 1950 | SM allowed for an improved OS when surgery allowed for a complete resection of metastasis | [35] |
| Yu | Retrospective study | 2015 | | Patients with CR displayed improved survival profiles than those achieving incomplete or no resection ($p = 0.001$)<br>T stage $\geq 3$ of the primary tumour, DFI of 12 or less months, and multiple organ metastases are significant factors of poor OS (HR = 1.88, $p = 0.015$, HR = 2.59, $p = 0.001$ and HR = 2.25, $p = 0.002$ respectively | [49] |

**Table 1** (continued)

| Study | Design | Year | N | Major outcomes | References |
|---|---|---|---|---|---|
| Brehmer | Retrospective database study | 2016 | 34 | patients with a metachronous metastatic disease achieved better overall survival rates than their synchronous controls(42)<br>a DFI < 12 months (p 0.0002) and multiple metastatic sites (p 0.04) predict a reduced overall survival (OS) after a neoadjuvant treatment with Bevacizumab, sunitinib, pazopanib or temsirolimus | [86] |
| Thiery-Villeumin | Retrospective 2-step approach: univariate, then multivariate analysis | 2017 | 224 | In patients undergoing first-line systemic therapy for mRCC, favourable and intermediate MSKCC risk groups, metastasectomy and N0 status upon initial presentation were associated with positive survival outcomes<br>Toxicity to first-line targeted therapy, time of disease control after first-line therapy, favourable and intermediate MSKCC risk groups were associated with positive survival outcomes in patients undergoing second-line therapy | [42] |
| Thomas et al | Matched controlled analysis | 2016 | 273 | No OS benefit was demonstrated for when metastasectomy was performed for mRCC with sarcomatoid dedifferentiation<br>Patients with positive lymph node status displayed worse survival profiles | [1] |
| Jakubowski et al | Retrospective cohort study | 2016 | 138 | Multiple metastasis, larger Metastasis size and interval from nephrectomy to metastasis as well as younger age and sarcomatoid features were stigmata of bad prognosis | [53] |
| Sun et al | Cohort study | 2018 | 6994 | patients treated with combined metastasectomy-targeted therapy (HR: 0. 86, 95% CI: 0.76–0.96, $p = 0.008$) vs. targeted monotherapy | [46] |
| Karam et al | Retrospective analysis | 2010 | 22 | Pre-SM with targeted therapies allowed for a stability in metastatic lesions, allowing for a better removal | [62] |

Consequently, being a significant predictor of survival in mRCC[33], single-site metastasectomy has been integrated to the NCCN guidelines both as an upfront treatment and as a best supportive care when relapse occurs, combined with ST [32, 34]. In a study by Thierry-Villeumin et al., it was demonstrated that, in patients receiving first-line ST for mRCC, those who underwent SM had a better OS (HR = 0.667(0.468–0.951) [33].

You et al. conducted a retrospective study to compare the PFS and OS in mRCC patients who underwent CR and those in whom this target was not met. Overall, 33 patients underwent complete resection of metastases whilst another 29 underwent an incomplete resection. Both groups were treated with adjuvant targeted therapy. The third group was exclusively treated with targeted monotherapy. The median PFS were 29.5 months (95% CI 17.3–41.7 months),

18.8 months (95% CI 11.7–25.9 months), and 14.8 months (95% CI 12.0–17.6 months) in the complete resection, incomplete resection and non-metastasectomy group ($p < 0.001$), respectively. The median OS was 92.5 months (95% CI 62.6–122.4 months) in the complete resection group, 29.6 months (95% CI 15.4–43.8 months) in the incomplete resection group, and 23.5 months (95% CI 18.9–28.1 months) in the non-metastasectomy group ($p < 0.001$) [34].

It was noteworthy that patients with an IMDC intermediate and poor risk group were respectively at 6- and 7.5-fold higher risk of poor survival outcomes than those undergoing metastasectomy with a favourable risk profile [34].

However, the meta-analysis by Zaid et al. proved that the survival benefits of complete resection of lesions extrapolate to non-solitary metastases as well [18].

In order to perform a head-to-head comparison between complete resection surgical metastasectomy and systemic monotherapy/combination of ST, Stuhler et al. [35] prospectively compared 80 patients who underwent complete surgical resection with 87 patients who underwent TKI monotherapy, 25 who underwent immunotherapy (IO) monotherapy (pembrolizumab) or combination therapy (nivolumab–ipilimumab), and 13 with an IO–TKI combination.

Data analysis showed that CSS was significantly higher in complete resection patients when compared to patients treated with TKIs (6.1 vs. 2.6 years, HR 0.45, $p < 0.001$) or an IO-based combination therapy as described earlier (6.1 vs. 3.5 years, HR 0.28, $p = 0.007$). Also, achieving complete resection after surgical metastasectomy improved CSS when compared to the pooled ST described earlier (5.8 vs. 3.1 years, HR 0.53, $p = 0.003$).

When analysing patients who had already received ST before surgery, a modest survival gain was already perceived since the Interferon-alpha and Interleukin-2 era [36]. However, despite the survival benefit observed with TKIs, the latter was similar to that seen with incomplete resection, with an OS not exceeding 27 months. Nonetheless, many patients included in this review had undergone or were still receiving protocols of ST when undergoing surgical metastasectomy, meaning that no rigorous head-to-head research work compared the outcomes of surgery to those of targeted therapies. In addition, only scarce information was available regarding the type and timing of introduction of ST. Therefore, a proper conclusion concerning the impact of combining ST with surgery could not be formulated (3–6).

The principle of adjuvant ST dates back to the interferon era. However, a more structured approach to the sequencing of systemic and local treatments was undertaken by the prospective keynote 506 trial [39] despite having a different primary outcome at sake.

The keynote 564 trial [40] is a phase 3, randomised, double-blind, international trial, randomising patients into adjuvant pembrolizumab versus placebo for 1 year following surgery for mRCC with high risk of recurrence, defined as tumour stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumour stage 3 or higher, regional lymph node metastasis, or stage M1 with no evidence of disease (NED) within a year after surgery. The trial demonstrated the efficacy of pembrolizumab to decrease the risk of recurrence by 32% with 77% of patients remaining alive and disease-free at 24 months, when compared to placebo (HR for recurrence or death, 0.68; 95% confidence interval [CI], 0.53–0.87; $p = 0.002$ [two-sided]).

When analysing the specific M1 NED population upon stratification, the benefit of adjuvant pembrolizumab was also demonstrated (HR 0.29; 95%CI 0.12–0.69). This benefit was maintained even when stratification was performed for the evaluation of synchronous or metachronous, lung or non-lung metastases [41, 42]. Based on this trial, the European Society of Medical Oncology (ESMO) recommends adjuvant pembrolizumab to oligometastatic patients after complete resection. These same guidelines strongly recommend a multimodal approach for M1 NED patients who relapse within 1 year after nephrectomy, consisting of programmed cell death protein 1 (PD-1)-based combination therapy (Grade I A) [43].

With the ongoing development of targeted therapies, a parallel surge in the local surgical treatment of metastases was noted. However, a sub-analysis of this phenomenon was able to show that the increase in combination therapy was not statistically significant from 2006 to 2013 [44]. A database study by Sun et al. included 1976 patients who underwent surgical metastasectomy, of which 43% had received targeted therapy. When SM patients were compared to patients treated conservatively, it was found that the median OS was 24.1 months for patients treated with metastasectomy vs. 18.9 months for patients undergoing conservative palliative therapy ($p < 0.001$). More importantly, the subanalysis of the patient cohort was able to prove that metastasectomy conferred a survival benefit in patients treated with combined metastasectomy-targeted therapy (HR: 0. 86, 95% CI: 0.76–0.96, $p = 0.008$) vs. targeted monotherapy, as well as in patients treated with surgical metastasectomy without targeted therapy vs. no surgery and no targeted ST (HR: 0.84, 95% CI: 0.75–0.94, $p = 0.004$) [44]. The major setback of this study is the lack of covariate matching for ST between the surgical and conservative treatment groups.

Dragomir et al. calculated the OS in patients with mRCC. The sample included 229 patients undergoing complete resection surgery and 803 who did not surgical metastasectomy. After balancing age, sex, pre-SM ST, primary tumour stage, sites of metastasis, histology and timing of metastases occurrence, between a patient cohort undergoing surgical metastasectomy in one branch and palliative therapy in the other, the research group demonstrated that CR improved

OS (81 months [interquartile range [IQR]: 58 – NR) vs. 61 months (IQR: 26 – NR), $p$ value = 0.0001) [45].

The study by Alt et al. [21], cited earlier, demonstrated the clinically significant survival (both CSS and OS) benefit of complete resection in mRCC patients since it managed to demonstrate that these patients had a CSS and OS of 4.8 and 4 years, respectively, whereas patients who did not achieve such status only averaged 1.3 years in terms of both CSS and OS ($p < 0.001$). More importantly, 45% of the included patients received a protocol of ST at some point, with only 6% of them assigned to a protocol of molecular targeted therapies. Only 28% of the patients achieving a complete remission status received ST vs 48.5% of patients in whom complete resection could not be achieved ($p < 0.001$). The initiation of ST improved CSS in the latter group from 1.1 to 1.6 years ($p = 0.01$) only.

In conclusion, obtaining a complete remission status through surgical metastasectomy seems to be of paramount importance for obtaining a CSS benefit in mRCC. In the absence of high-level evidence, the use of ST, either in the first-line or as a consolidation after SM remains a fundamental complementary approach.

Nonetheless, patient selection for surgery emerges as a limiting factor when it comes to the feasibility of surgery and survival results afterwards.

## Patient selection for metastasectomy

Table 2 provides the summary of evidence regarding patient selection for surgical metastasectomy.

In a retrospective single-centre study by Yu et al. [41], it was once again proven that patients with a complete resection of metastases after primary nephrectomy had better clinical and survival outcomes. Accordingly, patients with a complete resection of lesions achieved a 52-month OS whilst patients with incomplete resection only achieved an OS of 16 months and those with no resection an OS of 22 months ($p = 0.001$). A subsequent univariate analysis of data using the COX regression model showed that a T stage ≥ 3 of the primary tumour, a disease-free interval (DFI)—between the primary nephrectomy and the diagnosis of metachronous metastatic disease—of 12 or less months, and metastases to many organ sites proved to be significant factors of poor OS (HR = 1.88, $p = 0.015$, HR = 2.59, $p = 0.001$ and HR = 2.25, $p = 0.002$ respectively) [41].

The importance of the DFI has been explored throughout more recent studies, with sometimes smaller patient samples and lower levels of evidence. These were able to show that patients with a metachronous metastatic disease achieved better OS rates than their synchronous controls [46]. It has also been demonstrated that, in the era of targeted therapies, a DFI < 12 months ($p = 0.0002$) and multiple metastatic sites ($p = 0.04$) were still found to be strong predictors of reduced OS after an initial treatment with Bevacizumab, sunitinib, pazopanib or temsirolimus preceding the local surgical treatment of metastasis [1].

A systematic review of studies focussing on the role of surgical metastasectomy in the era of targeted therapies [25] provided even stronger evidence that the complete resection of all known disease led to a prolonged survival and lower all-cause mortality, and is thus a predictor of survival regardless of the patient performance status, when compared to incomplete resection [18]. The research work of Thiery-Villeumin [33] including patients with mRCC who have received first-line targeted therapies (mainly antiangiogenic agents), and second or third-line therapies with mTOR inhibitors or antiangiogenic agents found that median OS was improved in patients with a favourable Memorial Sloan Kettering Cancer Center (MSKCC) risk profile compared to intermediate or poor risk profiles (32.1 months [23.0–46.6] vs 22.4 [17.2–29.6] and 8.7 [5.3–12.7], respectively. Multivariate analysis performed on the aforementioned population found that favourable and intermediate MSKCC prognostic groups had a better OS (HR = 0.362 [0.207–0.630] and 0.561 [0.393 –0.801], respectively, $p$ value = 0.0004). Metastasectomy and an N0 status were also found to favourably correlate with OS (HR = 0.667 [0.468–0.951], $p$ value = 0.03); (HR = 0.715 [0.513–0.994], p-value = 0.049 respectively). When performing the same multivariate analysis on patients undergoing second-line treatment, it was found that treatment toxicity leading to the discontinuation of first-line therapy (HR = 0.298 [0.180–0.493], $p$ value < 10–4), time of disease control after the first-line treatment (HR = 0.961 [0.942–0.979], $p$ value = 2.10–4) and favourable and intermediate risks (HR = 0.461[0.252–0.843] and 0.936 [0.607–1.443], respectively, $p$ value = 0.02) were positively correlated with an enhanced survival.

In a retrospective study, Thomas et al. [47] and Jakubowski et al. [48] found that the benefit of surgical metastasectomy was less patent when sarcomatoid features were associated. In this particular entity, there was no difference between metastasectomy and non-surgical treatment whether it was for synchronous or asynchronous metastases (8.4 months for surgically treated patients vs. 8 months for those treated conservatively ($p = 0.35$)). When metastases occurred in an asynchronous pattern, no OS difference was found between surgical metastasectomy and conservative treatment. Once again, a positive lymph node status at nephrectomy was associated with a decreased survival upon multivariate analysis (HR 2.1, 95% CI 1.1–4.0, $p = 0.03$ and HR 3.3, 95% CI 1.2–9.2, $p = 0.02$ in both the synchronous and asynchronous subgroups, respectively). These studies shared a common limitation, through considering patients with single and multiple metastasis as equal, without proceeding to a balanced patient matching between the two groups [47].

**Table 2** Selection criteria for SM

| Study | year | Selection Criteria | References |
|---|---|---|---|
| Yu et al | 2015 | T stage ≥ 3 of the primary tumour, DFI ≤ 12 months, and metastases to many organ sites yield poor overall survival after (HR = 1.88, $p = 0.015$, HR = 2.59, $p = 0.001$ and HR = 2.25, $p = 0.002$ respectively) | [49] |
| Tosco et al | 2013 | metachronous metastatic disease showed better survival profiles than synchronous disease | [52] |
| Brehmer et al | 2016 | a DFI < 12 months ($p = 0.0002$) and multiple metastatic sites ($p = 0.04$) predicted reduced overall survival (OS) after an initial treatment with Bevacizumab, sunitinib, pazopanib or temsirolimus preceding SM | [2] |
| Zaid et al<br>Ouzaid et al | 2017<br>2019 | CR of all known disease lead to a prolonged survival and lower all-cause mortality, regardless of patient performance status | [25] |
| Thierry-Villeumin et al | 2018 | Metastasectomy and an N0 status show enhanced overall survival (p value = 0.03 and 0.049 respectively)<br>The best survival outcomes were found in patients with favourable or intermediate MSKCC risk<br>For second-line therapy, treatment toxicity leading to the discontinuation of first-line therapy, time of disease control after the first-line treatment (p-value = 2.10–4) and favourable and intermediate risks ( p-value = 0.02) were positively correlated to an enhanced survival | [42] |
| Thomas et al | 2016 | Smaller benefit surgical metastasectomy when sarcomatoid features were associated<br>No correlation of metastasis synchronicity with outcomes after SM<br>A positive lymph node status at nephrectomy was associated with a decreased survival for synchronous ($p = 0.03$) and asynchronous ($p = 0.02$) disease | [1] |
| Jakubowski et al | 2016 | Removal of more than one tumour from a single organ site had a higher risk of disease recurrence ($p = 0.003$)<br>Older patients and those with a prolonged DFI showed a decreased risk of recurrence after SM( $p = 0.012$, 0.023, respectively)<br>Sarcomatoid dedifferentiation was a bad prognostic feature for CSS ($p = 0.037$) | [53] |
| Tosco et al | 2013 | primary tumour stage > 3 ($p < 0.01$), Fuhrman grade > 3 ($p < 0.03$), nonpulmonary metastases ($p < 0.03$), disease-free interval < 12 months ($p < 0.058$) and multiorgan metastases ($p < 0.04$) were indicators of poor CSS | [54] |
| Stühler et al | 2022 | Patients with bad performance status were more likely to undergo conservative systemic therapies as they are considered poor surgical candidates | [58] |
| Thomas et al.,<br>Patard et al<br>Rini et al | 2009<br>2009<br>2006 | More patients can become eligible for surgery after a primary response to first-line systemic therapy | [59–61] |
| Sun et al | 2018 | Management at an academic facility was more likely to include patients for SM ($p = 0.019$)<br>older age ($p = 0.004$), Afro-American ethnicity ($p < 0.001$) and other non-white races ($p < 0.013$),a pT2 ($p = 0.008$) and pT3 ($p = 0.001$) stages of primary tumours, non-clear cell histology ($p = 0.008$) and the administration of a pre-surgical targeted therapy ( $p < 0.001$) were less likely to undergo SM | [46] |
| Dragomir et al | 2020 | Patient age younger than 65 and metachronous metastasis were more likely to undergo SM<br>Patient comorbidity was not significantly correlated to the choice of treatment modality | [35] |
| Brehmer et al<br>Karam et al | 2016<br>2011 | Patients with residual disease after systemic therapy can be considered for SM | [2,62] |

In a retrospective cohort by Jakubowski et al. [48], including patients with synchronous and metachronous mRCC, it was demonstrated upon univariate analysis that patients who had more than one tumour removed from a single organ site, had a higher risk of disease recurrence (hazard ratio [HR] 1.95, 95%CI 1.26, 3.03, $p = 0.003$). Inversely, older patients and those with a prolonged interval between nephrectomy and metastasis showed a decreased risk of recurrence after the local treatment of metastases (HR 0.74 per 10 years, 95%CI 0.59, 0.94, $p = 0.012$, and HR 0.95 per 10 years, 95%CI 0.90, 0.99, $p = 0.023$, respectively). The size of the metastasis also influenced CSS with a HR of 1.18 per 1 cm (95%CI 1.07, 1.29, $p = 0.001$). The status and pattern of ST protocols were not clear for this cohort.

Therefore, for decision-making purposes, a risk stratification should be established for the estimation of the CSS benefit that can be obtained from surgical metastasectomy and cytoreductive nephrectomy for mRCC. A proposed method can be the Leuven–Udine stratification method where a score of 1 point is given for adverse prognostic factors: having a primary tumour stage > 3 (hazard ratio [HR]: 2.8; $p < 0.01$), Fuhrman grade > 3 (HR: 2.3; $p < 0.03$), non-pulmonary metastases (HR: 3.1; $p < 0.03$), disease-free interval < 12 months (HR: 2.3; $p < 0.058$) and multi-organ metastases (HR: 2.5; $p < 0.04$) and total scores are then stratified into groups. Patients with 0–1

(group A), 2 (group B), 3(group C) and 4–5 (group D) risk factors displayed different CSS profiles, worsening when cumulating risk factors. For instance, the 2- and 5-year CSS rates were 95.8% and 83.1%, 89.9 and 56.4%, 65.6% and 32.6%, and 24.7% and 0%, respectively, for groups A, B, C, and D ($p < 0.0001$). This stratification according to risk groups may be a useful tool to stratify patients in order to determine those who would benefit most from surgical metastasectomy and those who would rather receive palliative ST [46].

Some authors suggested that patients with bad performance status were more likely to undergo conservative systemic therapies as they are considered poor surgical candidates [35].

The multimodal sequential treatment of mRCC has expanded the scope of surgery to some previously unresectable metastases owing to their size, number, or localization [1, 49–51].

Sun et al. [44] were able to show that patients' propensity to undergo surgical metastasectomy was higher if they were managed at an academic facility (odds ratio [OR]: 1.57, 95% confidence interval [CI] 1.20–2.06, $p = 0.001$), in more recent years (OR 1.03, 95% CI 1.01–1.05, $p = 0.019$). On the other hand, older age (OR: 0.99, 95% CI: 0.98–1.00, $p = 0.004$), Afro-American ethnicity (OR: 0.65, 95% CI: 0.51–0.82, $p < 0.001$) and other non-white races (OR: 0.89, 95% CI: 0.61–0.94, $p < 0.013$), pT2 (OR: 0.77, 95% CI: 0.63–0.93, $p = 0.008$) and pT3 (OR: 0.76, 95% CI: 0.65–0.89, $p = 0.001$) stages of primary tumours, non-clear cell histology (OR 0.81, 95% CI 0.70–0.95, $p = 0.008$) and the administration of a neo-adjuvant targeted therapy (OR: 0.72, 95% CI: 0.63–0.82, $p < 0.001$) were less likely to undergo surgical metastasectomy. Using a propensity score, Dragomir et al. also managed to show that patient age younger than 65 and metachronous metastases were more likely to undergo surgical metastasectomy. Patient comorbidity was not significantly correlated to the choice of treatment modality [45].

Selecting the right candidate for surgical metastasectomy emerges to be of upmost importance. This selection relies on both patient and tumour characteristics. Patients are more likely to benefit from surgery when they have a preserved performance status, good or intermediate prognostic risk factors, a prolonged DFI after initial nephrectomy and a solitary lesion or oligometastatic disease. Low tumour grade and the absence of sarcomatoïd features are also important selection criteria [1, 25, 27, 30, 52].

## Conclusion

In summary, in the era of combined therapies, encompassing targeted and IO therapies, surgical metastasectomy has to be integrated into a multimodal strategy with two main approaches. Thus, consolidation surgical metastasectomy can be proposed after upfront targeted therapies in the therapeutic strategy of patients with metastases that are deemed unresectable due to their number, size or proximity to vital structures. On the other hand, upfront surgical metastasectomy can be a viable option, leaving targeted therapies for treatment consolidation or the management of relapses or progression. The latter strategy aims at reducing treatment toxicity and postpone drug resistance and morbidity without a compromise in survival outcomes, whilst sparing a therapeutic strategy for relapse. The main task remains in selecting the best candidates for this multimodal therapy: preserved performance status, a metastatic status that can ensure a complete resection of lesions, a favourable pathology namely a low tumorous grade, absence of sarcomatoid features and favourable prognostic group and disease-free interval. [1, 53, 54]

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## Declarations

**Conflict of interest** Abi Tayeh Georges, Alkassis Marwan, De La Taille Alexandre, Vordos Dimitri, Champy Cécile Maud and Pelegrin Tiphaine declare that they have no competing interests. INGELS Alexandre: Intuitive Surgical, BMS, IPSEN. The authors have no competing interests to declare that are relevant to the content of this article.

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