



# Pulmonary metastasectomy in renal cell carcinoma: a mainstay of multidisciplinary treatment

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**Abstract:** Renal cell carcinoma (RCC) remains a public health issue and seems to be increasing. A significant proportion of RCC patients will develop pulmonary metastasis at some point in their evolution. In this review, we aimed to update the surgical management of pulmonary metastases as well as systemic therapy, including targeted therapies, according to recent data in the literature. We retrospectively reviewed studies evaluating the benefit of pulmonary metastasectomy in RCC patients and evaluating the place of different chemotherapies, targeted therapies and immunotherapies through November 1, 2019. Several retrospective studies have shown the benefit of pulmonary metastasectomy in metastatic RCC (mRCC), most in a situation with only pulmonary metastases. According to the prognostic criteria of the IMDC risk model, the patient is classified into a prognostic group to identify the best systemic treatment. With the development of targeted therapies, the modalities are multiple and may involve tyrosine kinase inhibitors/checkpoint inhibitors and soon vaccine therapy or CAR-T cells. At the local level, in patients who cannot benefit from surgery, stereotactic radiotherapy or radiofrequency has a place to be considered. Although there is a lack of a randomized study, pulmonary metastasectomy appears to be feasible and effective. The place and modalities of systemic therapies in the era of targeted therapies remain to be more clearly defined.

**Keywords:** Renal cell carcinoma (RCC); lung; metastasis

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## Introduction

RCC remains a main cause of cancer-related deaths. Indeed, during the last 2 decades in the United States, the incidence of RCC has increased with an estimated 73,820 in 2019 (1) in comparison with 62,700 cases in 2016 (2).

As in many other cancers, patients already have metastases at the time of diagnosis in a significant number of cases. Indeed, approximately one-third of patients present mRCC (3). Moreover, 20–30% of patients with localized RCC who benefit from curative surgery will exhibit metastatic spread during follow-up (4–6).

In mRCC, 7% of lung metastases are present at the

time of diagnosis according to a recent publication (7). In 50% to 60% of cases, in patients who have recurrences after curative surgery, recurrence is localized in the lung parenchyma (5,6).

Historically, the most commonly used chemotherapies for renal cell carcinoma were interferon alfa and interleukin-2. Despite a low response rate of 12% and a high level of toxicity, interferon alfa was the cornerstone of treatment in metastatic RCC (8). High-dose (HD) interleukin-2 is associated with cardiovascular toxicity that restricts clinical use, despite complete response in 5% of patients treated for advanced RCC (9). Interleukin-2 received FDA approval in mRCC in 1992. In fact, there is no predictive biomarker for

the responses of HD interleukin-2 (10).

Recent advances in the field of molecular biology have led to the use of tyrosine kinase inhibitors. First, multityrosine kinase inhibitors were developed in the early 2000s with FDA approval in 2005 and 2006 for sorafenib and sunitinib, respectively. Then, specific vascular endothelial growth factor (VEGF) inhibitors were developed, and FDA approval quickly followed (bevacizumab). In a second step, research on tyrosine kinase inhibitors made it possible to specifically target the mammalian target of rapamycin (mTOR) as temsirolimus. In a multicenter phase III trial reported in 2007, temsirolimus improved overall survival among patients with mRCC and poor prognosis compared with interferon alpha (11).

Recently, a paradigm shift in cancer control has been achieved through immunotherapy, which also has a benefit for patients with advanced RCC, first reported in 2015 (12).

We will now discuss the management and benefit of pulmonary metastasectomy in advanced RCC in light of the latest publications. Second, we will detail the targeted therapies and their evolution in advanced renal cell carcinoma patients.

## Materials and methods

The Medline® database was searched for studies evaluating the benefit of pulmonary metastasectomy in RCC and evaluating the place of different chemotherapies, targeted therapies and immunotherapies through November 1, 2019.

## Results

### Prognostic factors

The International Metastatic RCC Database Consortium (IMDC) Risk Model is currently used to evaluate prognosis in patients with mRCC. Indeed, by using 6 clinical and biological factors, this model makes it possible to classify patients into 3 categories: favorable, intermediate, and poor (13). In this updated model, the median overall survival was 43 months, 22 months and 8 months, respectively in the favorable, intermediate and poor groups. According to the National Comprehensive Cancer Network, the choice of first-line systemic therapy based on the different groups is as follows:

- Intermediate or poor risk: cabozantinib (multityrosine kinase inhibitor) or nivolumab associated with ipilimumab (dual checkpoint inhibitor).

- Favorable risk: pazopanib (multityrosine kinase inhibitor) or sunitinib (multityrosine kinase inhibitor).

### Surgery

Systemic therapy can improve overall survival in mRCC but involves exceptionally prolonged remission or cure times. As such, surgical management of mRCC has to be considered. There is no randomized trial to assess the role of metastasectomy in mRCC, although there are many retrospective studies. The first metastasectomy for mRCC was reported in 1939 (14).

In a study published in 2019, the authors reported 44 studies concerning more than 4,000 patients and evaluated the clinical benefits and the selection of patients.

Rather than listing them, specifying the number of patients included, metastasis sites and 5-year survival, we have chosen to focus on studies with pulmonary metastases and present the most interesting ones here.

The two most recent studies were published in 2017 and 2019, including 27 patients with metastatic RCC and 35 with metastatic clear cell renal carcinoma (15,16). The 5-year survival data were 75% and 44.9%, respectively. In these two studies, only patients with lung metastases were included, and the dimension of pulmonary metastases was an independent prognostic factor for OS and DFS. Another recent study focused on specific renal histology: renal cell carcinoma with sarcomatoid dedifferentiation. Indeed, Thomas *et al.*, in this matched controlled analysis including 80 patients, did not find a benefit of metastasectomy for this histological type (P=0.35) (17).

Only a few studies have compared metastasectomy with a control arm, either versus no surgery or versus targeted therapy only, but these studies concerned patients with multisite metastases (18). In 2017, a meta-analysis including 1,447 patients through 16 studies reported 43% 5-year survival and highlighted poor prognostic factors such as lymph node involvement (LNI) of primary RCC [hazard ratio (HR) 3.44, confidence interval (CI): 1.78–6.67, P=0.001], incomplete resection of metastases (HR 3.74, 95% CI: 2.49–5.61, P=0.001), multiple metastases, larger metastases, LNI of metastases, synchronous metastases and short DFI (19). One study looked more closely at mediastinal LNI and observed LNI as a prognostic factor in univariate and multivariate analysis (median survival: 107 *vs.* 37 months, P=0.003; HR 0.384, 95% CI: 0.179–0.825, P=0.01, respectively) (20). However, even in patients with node involvement, pulmonary metastasectomy should be

considered regarding a median survival of 37 months (20).

Finally, all these studies argue for the safety and feasibility of pulmonary metastasectomy with favorable outcomes; however, the selection of patients needs to be optimized.

### Systemic therapy

#### Nonspecific therapy

As previously seen, the first chemotherapy used in mRCC was interferon alfa, first reported in 1986 (21). Throughout the years and the evolution of RCC treatment, interferon has been used in monotherapy or in association with vinblastine (21), bevacizumab (22) and temsirolimus (11). However, interferon has been surpassed by sunitinib in monotherapy since 2007 (23).

Until 2006 and the development of molecular biological techniques, a high dose of interleukin-2, which consists of a nonspecific immunotherapy, was a standard therapy for mRCC. Similar to interferon alfa, interleukin-2 therapy has been surpassed by therapy with tyrosine kinase inhibitors. Even if the recommended first-line current therapies have been previously used according to the IMDC risk model and do not include interleukin-2, it remains a first-line option in selected, favorable-risk younger patients, with good performance status (24).

#### Targeted therapies

Advances in the field of molecular biology led to the development of molecules that inhibit the action of tyrosine kinases in the mid-2000s. Tyrosine kinases are intracellular or membranous molecules. These molecules may be specific to tyrosine kinase or have several cellular targets.

Sunitinib is currently the most used multi-tyrosine kinase inhibitor. Indeed, its cellular targets are VEGF, platelet-derived growth factor (PDGF) and CD117. Its superiority in monotherapy has been demonstrated versus interferon alfa, and sunitinib is still recommended in first-line therapy in favorable-risk patients (23).

Similarly, pazopanib is a recent multikinase angiogenesis inhibitor recommended in favorable-risk patients with metastatic RCC. In a randomized, phase III trial including 1,110 patients, Motzer *et al.* demonstrated noninferiority between pazopanib and sunitinib. Moreover, due to different side effects, patients treated with pazopanib exhibited a better quality of life (25).

A specific VEGF tyrosine kinase inhibitor was first used in association with interferon alfa. In the report of

Escudier *et al.*, bevacizumab and interferon alfa significantly improved progression-free survival (HR 0.63, 95% CI: 0.52–0.75,  $P=0.0001$ ) (22). There was no benefit in terms of overall survival. Currently, bevacizumab and interferon alfa are not recommended for first-line therapy.

In the late 2000s, at the same time as the development of tyrosine kinase inhibitors, molecules inhibiting the mTOR pathway were developed. Despite encouraging initial trials, compared to interferon alpha (11), temsirolimus is no longer recommended as a first-line treatment for patients with a favorable prognosis, intermediate prognosis or poor prognosis. A recent study comparing temsirolimus and pazopanib in high-risk patients showed the limitations of these two molecules in this specific population (26). However, temsirolimus or everolimus may still be an alternative treatment for patients in second-line treatment.

#### Immunotherapy

In the beginning of the 2010s, immunotherapy demonstrated clinical benefit in uncontrolled studies in previously treated patients with advanced RCC. In 2015, Motzer *et al.* demonstrated the clinical benefit of nivolumab versus everolimus in a randomized, controlled study (12). Indeed, in mRCC patients who previously received antiangiogenic therapy (three or fewer systemic therapies) and who exhibited progressive disease, nivolumab was better than everolimus in terms of overall survival (HR 0.73, 95% CI: 0.57–0.93,  $P=0.0018$ ) and had a greater objective response rate (ORR) in nivolumab (25%) than everolimus (5%, odds ratio 5.98, 95% CI: 3.68–9.72,  $P<0.001$ ). No difference was observed in terms of PFD.

Moreover, the most commonly used checkpoint inhibitors are programmed cell death 1 (PD-1) inhibitors such as nivolumab. An interesting strategy is to combine them with other checkpoint inhibitors, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, to achieve a synergistic effect. This was done by Motzer *et al.* in 2018 (27). Indeed, in patients who are not receiving prior treatment, with intermediate and poor risk, the combination of nivolumab and ipilimumab has shown real clinical interest. This phase III trial compared nivolumab and ipilimumab versus sunitinib in previously untreated clear cell renal carcinoma; a total of 1,096 patients were randomly assigned to receive nivolumab and ipilimumab or sunitinib.

In his latest paper, Motzer *et al.* confirmed the clinical data of the combination in terms of overall mortality, progression-free survival and response rate in the same cohort of 1096 patients with extended follow-up (28). This

trial, whose follow-up has been extended (median follow-up 32.4 months, IQR 13.4–36.3), also investigated the side effects of combination immunotherapy treatment. The most common side effects were increased lipase (10%), increased amylase (6%), and increased alanine aminotransferase (5%).

However, in the era of targeted therapies and immunotherapy, drug costs are rising dramatically. For this reason, it is necessary to evaluate not only the effectiveness of a treatment but also its cost. In a recent study, the combination of nivolumab and ipilimumab was evaluated in terms of cost-effectiveness versus sunitinib (29). In this study, the combination of immunotherapy appears to have a cost benefit related to the efficacy of the product. In addition, this cost-effectiveness seems to be most interesting in patients expressing at least 1% of programmed cell death ligand (PDL1). Finally, the development of new checkpoint inhibitors makes it possible to imagine new therapeutic combinations (30).

### Vaccine therapy

Vaccine-mediated immunotherapy shows promising advances in many cancers, particularly in non-small cell lung cancer (NSCLC) (31). To date, the most important trial was reported in the *Lancet* journal in 2016. The addition of a multipeptide vaccine to sunitinib in a multicenter randomized controlled trial involving 339 patients did not show any mortality benefits (32). In addition, there appeared to be more adverse events in the vaccine group. This study was conducted in patients with advanced or metastatic renal cancer. The vaccine-mediated immune response must be improved before new tests in renal cancer can be planned.

### CAR-T cells

Chimeric antigen receptor-modified T (CAR-T) cells have demonstrated promising effects in hematologic malignancies (33,34). However, their effects in solid tumors remain disappointing. A new strategy could consist of systemic chemotherapy as a multityrosine kinase inhibitor. For this purpose, an *in vitro* study showed an interesting effect on RCC lung metastasis in a mouse model. Indeed, CAIX-specific CAR-T cells in association with sunitinib can significantly enhance antitumor effects (35). To date, there is no clinical study with such an association.

### Stereotactic radiotherapy

As we have seen previously, lung metastasectomy for metastatic renal cancer provides good local control and

interesting 3- and 5-year survival rates. However, in a few cases, due to reduced performance status or comorbidities and some pulmonary metastases that may be difficult to resect, patients are not eligible for surgery.

Historically, renal cancer is considered a “radioresistant” histological type. However, pulmonary metastases appear to be more sensitive when using hypofractionated, high-dose stereotactic body radiotherapy (SBRT). The results are encouraging for this type of nonoperable patient (36–38) because SBRT delivers a high dose to the target area while preserving surrounding tissue, thus inducing lower toxicity. A recent study involving 46 patients and 67 pulmonary metastases showed that stereotactic radiotherapy allows good local control, and in terms of overall survival, interesting results with a mortality rate at 1 year of 84.3% and at 3 years of 43.8% (39). In this study, the toxicity associated with SBRT was interestingly low.

Another approach, published in a recent study, was to collect all the data on stereotaxis on pulmonary metastases of any site and to deduce a radiosensitivity index (RSI) according to the histological type. This study proposes adjustments of the SBRT dose administered according to the primary histological type of lung metastases to optimize the treatment efficacy (40).

### Radiofrequency

The scanner-guided radiofrequency technique for pulmonary metastases of renal cell carcinoma gave rise to several publications in the late 2000s (41,42). These publications mainly focused on the feasibility and adverse events; we can also mention the high risk of pneumothorax (42%) (41).

However, we must note that this technique has been gradually abandoned. Indeed, since 2016, no further publications mentioning the radiofrequency of RCC lung metastases have been reported. In addition, in a letter to the editor Detterbeck FC points out some inconsistencies in Huo’s publication (43), which may lead to the abandonment of the technique. In a significant number of cases (33%), radiofrequency had been carried out for palliative purposes on nonsymptomatic patients without curative intent.

To date, there is no long-term follow-up trial or controlled trial for radiofrequency in metastases in RCC.

### Discussion

As of 2019, we had many retrospective reports highlighting prolonged median survival with pulmonary metastasectomy,

but we are still lacking a well-designed prospective study.

The current challenge in terms of chemotherapy remains the choice of second-line therapy in the case of failure of the first-line therapy according to the criteria seen above.

In mRCC patients who experience rapidly progressive disease (PD) on treatment with sunitinib, there is currently no evidence to prefer one treatment or another in the second-line therapy (44). The question remains more relevant than ever, and an answer could probably be found in part thanks to advances in immunotherapy.

More and more multimodal combinations are developing in the field of immunotherapy, and there will probably be new advances in CAR-T cell therapy or oncolytic vaccines, presumably in a configuration in combination with checkpoint inhibitors.

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