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
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 multiproptide 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.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Khosro Hekmat) for the series “Pulmonary Metastases” published in Journal of Thoracic Disease. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-2019-pm-10). The series “Pulmonary Metastases” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

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

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
3. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol 2001;166:1611-23.
4. Zisman A, Pantuck AJ, Wieder J, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 2002;20:4559-66.
5. Sandock DS, Seftel AD, Resnick MI. A new protocol for the followup of renal cell carcinoma based on pathological stage. J Urol 1995;154:28-31.
6. Rabinovitch RA, Zelefsky MJ, Gaynor JJ, et al. Patterns of failure following surgical resection of renal cell carcinoma: implications for adjuvant local and systemic therapy. J Clin Oncol 1994;12:206-12.
7. Chandrasekar T, Klaassen Z, Goldberg H, et al. Metastatic renal cell carcinoma: Patterns and predictors of metastases-A contemporary population-based series. Urol Oncol 2017;35:661.e7-661.e14.
8. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. N Engl J Med 1996;335:865-75.
9. Klapper JA, Downey SG, Smith FO, et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma : a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. Cancer 2008;113:293-301.
10. McDermott DF, Cheng S-C, Signoretti S, et al. The high-dose aldesleukin «select» trial: a trial to prospectively validate predictive models of response to treatment in patients with metastatic renal cell carcinoma. Clin Cancer Res 2015;21:561-8.
11. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-81.
12. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
13. Heng DYC, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol 2013;14:141-8.
14. Barney JD, Churchill EJ. Adenocarcinoma of the Kidney with Metastasis to the Lung: Cured by Nephrectomy and Lobectomy. J Urol 1939;42:269-76.

15. Meacci E, Nachira D, Congedo MT, et al. Lung metastasectomy following kidney tumors: outcomes and prognostic factors from a single-center experience. J Thorac Dis 2017;9:S1267-72.

16. Procházková K, Vodička J, Fichtl J, et al. Outcomes for Patients after Resection of Pulmonary Metastases from Clear Cell Renal Cell Carcinoma: 18 Years of Experience. Urol Int 2019;103:297-302.

17. Thomas AZ, Adibi M, Slack RS, et al. The Role of Metastasectomy in Patients with Renal Cell Carcinoma with Sarcomatoid Dedifferentiation: A Matched Controlled Analysis. J Urol 2016;196:678-84.

18. Yu X, Wang B, Li X, et al. The Significance of Metastasectomy in Patients with Metastatic Renal Cell Carcinoma in the Era of Targeted Therapy. BioMed Res Int 2015;2015:176373.

19. Zhao Y, Li J, Li C, et al. Prognostic factors for overall survival after lung metastasectomy in renal cell cancer patients: A systematic review and meta-analysis. Int J Surg 2017;41:70-7.

20. Renaud S, Falcoz PE, Alifano M, et al. Systematic lymph node dissection in lung metastasectomy of renal cell carcinoma: an 18 years of experience. J Surg Oncol 2014;109:823-9.

21. Fosså SD, de Garis ST, Heier MS, et al. Recombinant interferon alfa-2a with or without vinblastine in metastatic renal cell carcinoma. Cancer 1986;57:1700-4.

22. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103-11.

23. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.

24. Tegos T, Tegos K, Dimitriadou A, et al. Current and emerging first-line systemic therapies in metastatic clear-cell renal cell carcinoma. J BUON 2019;24:1340-53.

25. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722-31.

26. Tännir NM, Msaouel P, Ross JA, et al. Temsirolimus versus Pazopanib (TemPa) in Patients with Advanced Clear-cell Renal Cell Carcinoma and Poor-risk Features: A Randomized Phase II Trial. Eur Urol Oncol 2020;3:687-94.

27. Motzer RJ, Tännir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-90.

28. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol 2019;20:1370-85.

29. Wan X, Zhang Y, Tan C, et al. First-line Nivolumab Plus Ipilimumab vs Sunitinib for Metastatic Renal Cell Carcinoma: A Cost-effectiveness Analysis. JAMA Oncol 2019;5:491-6.

30. Vaishampayan U, Schöffski P, Ravaud A, et al. Avelumab monotherapy as first-line or second-line treatment in patients with metastatic renal cell carcinoma: phase Ib results from the JAVELIN Solid Tumor trial. J Immunother Cancer 2019;7:275.

31. Quoix E, Ramlau R, Westeel V, et al. Therapeutic vaccination with TG4010 and first-line chemotherapy in advanced non-small-cell lung cancer: a controlled phase 2B trial. Lancet Oncol 2011;12:1125-33.

32. Rini BI, Stenzl A, Zdrojowy R, et al. IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol 2016;17:1599-611.

33. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med 2017;377:2531-44.

34. Park JH, Rivière I, Gonen M, et al. Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia. N Engl J Med 2018;378:449-59.

35. Li H, Ding J, Lu M, et al. CAIX-specific CAR-T Cells and Sunitinib Show Synergistic Effects Against Metastatic Renal Cancer Models. J Immunother 2020;43:16-28.

36. Wang CJ, Christie A, Lin M-H, et al. Safety and Efficacy of Stereotactic Ablative Radiation Therapy for Renal Cell Carcinoma Extracranial Metastases. Int J Radiat Oncol Biol Phys 2017;98:91-100.

37. Svedman C, Sandström P, Pisa P, et al. A prospective Phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma. Acta Oncol 2006;45:870-5.

38. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell
carcinoma. Int J Radiat Oncol Biol Phys 2012;82:1744-8.
39. Hoerner-Rieber J, Duma M, Blanck O, et al. Stereotactic body radiotherapy (SBRT) for pulmonary metastases from renal cell carcinoma-a multicenter analysis of the German working group « Stereotactic Radiotherapy ». J Thorac Dis 2017;9:e4512-22.
40. Ahmed KA, Scott JG, Arrington JA, et al. Radiosensitivity of Lung Metastases by Primary Histology and Implications for Stereotactic Body Radiation Therapy Using the Genomically Adjusted Radiation Dose. J Thorac Oncol 2018;13:1121-7.
41. Shu Yan Huo A, Lawson Morris D, King J, et al. Use of percutaneous radiofrequency ablation in pulmonary metastases from renal cell carcinoma. Ann Surg Oncol 2009;16:3169-75.
42. Soga N, Yamakado K, Gohara H, et al. Percutaneous radiofrequency ablation for unresectable pulmonary metastases from renal cell carcinoma. BJU Int 2009;104:790-4.
43. Detterbeck FC. Radiofrequency ablation (RFA) of pulmonary metastases: technical success vs. actual benefit. Ann Surg Oncol 2010;17:1214; author reply 1215.
44. Bersanelli M, Iacovelli R, Buti S, et al. Metastatic Renal Cell Carcinoma Rapidly Progressive to Sunitinib: What to Do Next? Eur Urol Oncol 2021;4:274-81.