Original Article

Surgery for thoracic oligoprogression in metastatic renal cell cancer in the era of new systemic therapies

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Background: Novel systemic therapies have improved response rates and survival in metastatic renal cell cancer (mRCC) and are considered standard of care for this entity. However, complete remission (CR) is rare and often oligoprogression is observed. Here, we analyse the role of surgery for oligoprogressive lesions in mRCC.

Methods: We retrospectively analyzed all patients who underwent surgery for thoracic oligoprogressive lesions of mRCC after receiving systemic therapy including immunotherapy, tyrosine kinase inhibitors (TKI), and/or multikinase inhibitors at our institution between 2007 and 2021 regarding treatment modalities, progression-free survival (PFS) and overall survival (OS).

Results: Ten patients with oligoprogressive mRCC were included. The median interval between nephrectomy and oligoprogression was 65 months (range, 16–167). Median PFS after surgery for oligoprogression was 10 months (range, 2–29) and median OS after resection 24 months (range, 2–73). In 4 patients, CR was achieved of whom three showed no progression at last follow-up (PFS median 15 months, range, 10–29). In 6 patients, removal of the progressive site resulted in stable disease (SD) for a median of 4 months (range, 2–29), before 4 of them progressed.

Conclusions: In selected cases, surgery can lead to sustained disease control in patients with oligoprogressive mRCC after systemic treatment including immunotherapy and novel treatment agents.

Keywords: Metastasized renal cell cancer (mRCC); oligoprogressive disease (OPD); local ablative therapy

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Introduction

Renal cell cancer (RCC) accounts for approximately 4% of all solid tumors and constitutes 1.8% of all global cancer deaths. One third of the patients presents with metastatic disease at initial diagnosis and 30% of the remaining patients will develop metastases during the course of disease (1,2). The lungs are most commonly affected, with lung metastases occurring in 48% of all patients with RCC (2).

Novel systemic therapies because of improving progression-free survival (PFS), response rates and, in some registration studies, overall survival (OS) are considered the standard of care in metastatic renal cell cancer (mRCC) (3-8). After cytoreductive nephrectomy, tyrosine kinase inhibitors (TKIs), anti-VEGF antibodies, mTOR inhibitors and immune checkpoint inhibitors

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are administered as monotherapies or in combinations, based on the patients prognostic score and the cancers histology (8). However, complete remission (CR) is rarely achieved and oligoprogression is often observed under systemic treatment (9).

Oligoprogression is defined as anatomically restricted tumor progression in an otherwise controlled disease (2). Its pathogenesis is complex, but is thought to involve tumor heterogeneity, which allows individual metastases to develop mutations, making them resistant against the systemic therapy applied (10). Local ablative therapies such as surgery or stereotactic radiotherapy can help achieve CR by eliminating progressive lesions, which do not respond to systemic therapy.

There have been several studies on local ablative therapies such as stereotactic radiotherapy for oligometastatic lesions in mRCC, which have shown encouraging results. In their meta-analysis on pooled data from 28 available studies (SABR ORCA), Zaorsky and colleagues reported a 1-year local control rate of 89.1% and a 1-year OS of 86.8% for extracranial oligometastatic lesions as well as a 1-year-local control rate of 90.1% and a 1-year OS of 49.7% for intracranial lesions (11). For stereotactic body radiotherapy (SBRT) for oligometastatic lesions occurring under treatment with TKI, Cheung and colleagues reported a 1-year local control of the irradiated tumors of 93%, a median PFS after SBRT of 9.3 months and a 1-year OS of 92% in their prospective multi-center study on 37 patients with 57 oligoprogressive tumors (12).

For surgical metastasectomy in mRCC, a meta-analysis on 10 studies by Naito and colleagues shows an advantage in OS for patients with complete metastasectomy compared to patients that did not undergo metastasectomy. However, the authors caution, that because all studies were conducted retrospectively, results might be influenced by selection bias (13). Data on metastasectomy for oligoprogressive disease (OPD) after systemic treatment for mRCC are rare and there are no studies focussing exclusively on surgical treatment of this entity.

As disease courses are often complex and treatment modalities and regimens vary greatly, we assessed individual trajectories to elucidate possible effects of thoracic surgical resection. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1120/rc).

Highlight box

Key findings

- Resection of oligoprogressive lesions after systemic therapy, including immunotherapy and novel treatment agents, can lead to sustained disease control in patients with metastasized renal cell cancer (mRCC).

What is known and what is new?

- Recent studies have shown that stereotactic radiotherapy of oligoprogressive lesions in mRCC after systemic therapy can achieve excellent 1-year local control rates.
- In this study we show, that resection of oligoprogressive lesions can provide prolonged survival and sustained disease control in patients with mRCC after systemic therapy

What is the implication, and what should change now?

- Further prospective randomized trials as well as (molecular) analysis of resected specimen are needed to identify patients, who will benefit from local treatment and determine the extent of improvement of disease control and survival.

Methods

This retrospective observational study was conducted at the Department of Thoracic Surgery at the Medical Center - University of Freiburg, Germany. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of the University of Freiburg (No. 21-1345) and individual consent for this retrospective analysis was waived.

At our institution, patients with RCC first present to the Department of Urology. Surgical and systemic treatment is decided upon according to international and national guidelines in a multidisciplinary tumor board. In case of thoracic oligoprogressive or oligometastatic disease (OMD), the patient is presented to the Department of Thoracic Surgery for evaluation of resection. In general, computed tomography of the chest and abdomen are performed every three months during treatment to monitor tumor response, complemented by PET-scan, if tumor progress is suspected. In case of CR, follow-up scans are performed every 6 to 12 months.

Patient population

We included all patients aged 18 years or older at the time of presentation, who underwent surgery at our institution between April 2007 and August 2021 for thoracic oligoprogressive or oligometastatic lesions after systemic treatment for mRCC. No exclusion criteria were applied. Data were collected by manual search of the institutional

database.

Outcome parameters

Primary objective of our study was to analyse the role of surgery for OPD and OMD after systemic treatment for mRCC. Therefore, the primary outcome parameter for this study was OS after resection of the oligoprogressive or oligometastatic lesion. Secondary outcome parameters included disease-free survival (DFS) and PFS after resection, applied systemic and local treatment modalities as well as surgery related mortality and morbidity.

Statistical analysis

Data were recorded in a database designed in Microsoft Office Excel (Microsoft, Redmond, WA, USA). Categorical and count data are presented as frequencies and percentages. Time intervals were calculated in days, end results were then converted to months by division by 30 and rounded to the nearest whole number. Additionally, timelines for the course of treatment and trajectory of disease were designed with Office Timeline Pro (Microsoft).

Results

Ten patients with metastasized clear-cell RCC were included in this study. Mean age at surgery for oligoprogressive or OMD was 65 years (SD 9). There were 8 (80%) male and 2 (20%) female patients. Six (60%) patients presented with metastases at initial diagnosis of RCC.

All patients had undergone systemic therapy prior to presentation for surgery of thoracic metastasis. Systemic therapy consisted of TKIs (N=10, 100%), mTOR-inhibitors (N=1, 10%) and/or immunotherapy (N=6, 60%). Systemic therapy was continued directly after resection of the oligoprogressive lesions in 3 (30%) patients. In total, 6 (60%) patients received systemic treatment during the further course of disease, of which 4 (40%) had immunotherapy.

In 4 (40%) patients, CR was achieved through resection of the oligoprogressive lesions of which 3 (30%) showed no sign of progression at last follow-up (PFS median 15 months; range, 10–29 months). In 6 patients, removal of the progressive site resulted in stable disease (SD) for a median of 4 months (range, 2–29 months), before 4 of them progressed, with one of these patients showing progress in the first follow-up after resection.

Median PFS after surgery for oligoprogression was 10 months (range, 2–29 months) and median OS 24 months (range, 2–73 months). Median OS calculated from start of systemic therapy until death or last follow-up was 73 months (range, 35–135 months). At the time of follow-up, 3 (30%) patients were deceased. Median follow-up calculated from nephrectomy was 93 months (range, 64–214 months).

The oligoprogressive lesions resected were located in the lung (N=8, 80%), thoracic lymph nodes (N=2, 20%) and chestwall (N=1, 10%). Seven (70%) wedge resections, 2 (20%) lymph node extirpations, 1 (10%) pneumonectomy and 1 (10%) chestwall resection were performed. In 1 (10%) case, resection was incomplete (R2) and additional stereotactic radiotherapy was administered. In all other patients, the lesions were removed with a sufficient safety margin (R0, N=9, 90%). Postoperatively, only 1 (10%) patient suffered a major complication (pleural empyema; Clavien-Dindo ≥ III) and 3 (30%) had minor complications (anaemia, vocal cord paresis, pneumonia; Clavien-Dindo ≤ II). None (N=0, 0%) of the patients died perioperatively. Patient and surgical characteristics are presented in *Table 1*. Individual disease trajectories presented in *Figure 1*.

Patient No. 1

SD with persisting left-sided pulmonary metastases was achieved under Axitinib. When three of these metastases progressed (OPD), all lesions were resected through left-sided wedge resections (maximal tumor size 1.7 cm) and CR was achieved.

Patient No. 2

Under treatment with Nivolumab, right-sided pulmonary metastases were stable, but left-sided pulmonary metastases progressed (OPD) and left-sided metastasectomy was indicated. The extent of the pulmonary metastasis required left pneumonectomy to achieve SD with persisting metastases on the right side. The resected tumor had a maximal size of 10 cm with endobronchial and pleural infiltration, but was completely resected. It was graded G3 for its predominantly rhabdoid cytomorphology.

Patient No. 3

In 2017, lung and chestwall metastases were resected. After bilateral pulmonary metastasectomy via wedge resection for

Table 1 Patients' characteristics

Parameter	Data
Patients	10
Age, years	65 [9.0]
Female	2 (20%)
Clear cell histology	10 (100%)
UICC VI at initial diagnosis RCC	6 (60%)
Time initial diagnosis RCC to diagnosis OPD	65 [16–167]
Immunotherapy before OPD	6 (60%)
Therapy leading to OPD	
Axitinib	1 (10%)
Nivolumab	4 (40%)
Sorafenib	2 (20%)
Everolimus	1 (10%)
Sunitinib	2 (20%)
Total duration of ST before OPD resection	29 [6–100]
Total duration of IT before OPD resection	5 [0–41]
Duration of OPD	4 [1–21]
Location of OPD	
Lung	8 (80%)
Lymph nodes	2 (20%)
Chestwall	1 (10%)
Procedure	
Pneumonectomy	1 (10%)
Pulmonary metastasectomy unilateral	6 (60%)
Pulmonary metastasectomy bilateral	1 (10%)
Lymph node extirpation	2 (20%)
Chestwall resection	1 (10%)
Additional radiotherapy	1 (10%)
R0-resection	9 (90%)
Morbidity	
Major complications (Clavien-Dindo ≥ III)	1 (10%)
Minor complications (Clavien-Dindo ≤ II)	3 (30%)
Continuation of ST directly after OPD resection	3 (30%)
Switch of ST after OPD resection	0 (0%)
PFS after OPD resection	10 [2–29]
OS after OPD resection	24 [2–73]
OS after nephrectomy	93 [64–214]
OS from start of ST	73 [35–135]
Total duration of ST after resection of OPD	6 [0–68]
Total duration of IT after resection of OPD	0 [0–20]
Patients receiving IT after resection of OPD	4 (40%)
Deceased	3 (30%)

Data were shown as n (%), mean [standard deviation] or median [range]. Time intervals were calculated in days, end results were then converted to months by division by 30 and rounded to the nearest whole number. UICC, union internationale contre le cancer; RCC, renal cell cancer; OPD, oligoprogressive disease; ST, systemic therapy; IT, immunotherapy; PFS, progression-free survival; OS, overall survival.

OMD with both metastases measuring 0.9 cm, Nivolumab was continued and the patient did not experience any recurrence until the last follow-up.

Patient No. 4

In 2014, pulmonary and localized pleural metastases were resected. During the further course of disease, the patient underwent stereotactic radiotherapy for hepatic and chestwall metastases. With right-sided thoracic lymph node extirpation in 2020, CR was achieved. The hilar lymph node metastasis did not penetrate its capsule and had a maximal size of 1.1 cm.

Patient No. 5

Because initial tumor progression was slow and according to the patients wishes, progressive disease (PD) was observed for a year, before it was treated with bilateral pulmonary metastasectomy and chemo-embolization (CE) of hepatic metastases as well as sunitinib and nivolumab. In 2017, right-sided chestwall resection with partial resection of the 5th rib and resection of the periosteum of the 4th rib was performed for OPD. The tumor was graded G3 and had a maximal size of 7 cm, infiltrating the bone as well as the soft tissue of the intercostal space, but was resected completely. Afterwards, the patient had a period of SD with persisting bone metastases, before he suffered tumor progression. The patient died in 2020 due to myocardial infarction.

Figure 1 Individual disease trajectories. These timelines show the individual course of treatment and trajectories of disease in patients undergoing resection of oligoprogressive lesions after systemic treatment of mRCC. mRCC, metastasized renal cell carcinoma; Nx, nephrectomy; PM, pulmonary metastasectomy; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; OPD, oligoprogressive disease; OMD, oligometastatic disease; Rx, resection; RT, radiotherapy; LN, lymph node; SIRT, selective internal radiation therapy; ADR, adrenal; PLE, pleural; HEP, hepatic; OTH, other; PUL, pulmonal; OSS, osseous; CUT, cutaneous; B, bilateral; L, leftsided; R, rightsided.

Patient No. 6

With right-sided pulmonary metastasectomy via wedge resections for OPD, CR was achieved. Maximal tumor size in four metastases was 2.9 cm and the tumors were graded G2. The patient suffered PD in 2014, for which he was first treated with resection of a small bowel metastasis, selective internal radiation therapy (SIRT) of hepatic metastases and systemic therapy with Sunitinib. When the patient was last assessed at our Medical Center, he suffered from massive tumor progression and very poor general condition. After treatment for pneumonia, best supportive care was agreed upon.

Patient No. 7

In this patient, one pulmonary metastasis could not be resected completely due to adhesions to the aortic arch and subclavian artery (R2). Stereotactic radiotherapy was administered, but the patient showed tumor progress in the first follow-up after resection and subsequently succumbed to the disease.

Patient No. 8

Before nephrectomy, two muscular metastases were already resected. Data is calculated beginning from the day of nephrectomy. Because initial tumor progression was very slow and discreet, PD was observed for more than two years, before Nivolumab was administered. After right-sided pulmonary metastasectomy via wedge resections for OPD, SD was achieved with persisting left-sided pulmonary metastases. The maximum tumor size was 0.6 cm and both metastases were graded G3.

Patient No. 9

With right-sided pulmonary metastasectomy via wedge resection for OPD, SD was achieved with persisting left-sided pulmonary metastases. The tumor had a maximum size of 0.8 cm and was graded G3. During the further course of disease, the patient developed a second RCC on the contralateral side, for which he eventually required resection of a chestwall metastasis.

Patient No. 10

In this patient, SD with persisting bone and liver metastases could be achieved through right-sided pulmonary metastasectomy via wedge-resection of one metastasis measuring 0.4 cm and lymph node extirpation of five lymph node metastases for OMD. The tumors were graded G3. After 3 months, the patient showed massive progression and eventually died due to sepsis.

Discussion

Oligoprogression in mRCC is a very heterogeneous and complex disease. While providing better response rates, novel systemic agents create a plethora of settings for which individualized approaches are required. Large studies, at least at this time, seem almost unfeasible and thus we analysed individual disease trajectories to further elucidate the role of radical local surgical resection in thoracic oligoprogression. Previous studies focussed mostly on the outcome of local ablative measures such as stereotactic radiotherapy.

Santini and colleagues assessed 55 patients with local ablative measures for OPD, of which 25 underwent resection of the oligoprogressive lesion. They focussed on the impact of systemic treatment and found that continuation of the same systemic therapy, after radical locoregional treatment of the progressive lesion was associated with a longer OS than a switch of systemic treatment (14).

With the resection of the oligoprogressive thoracic lesions, we could achieve local tumor control with CR or stable disease for all of our patients for a median of 10 months (PFS) after surgery. These results are comparable to those reported for patients undergoing SBRT for oligoprogressive lesions: in a prospective multi-center study on 37 patients undergoing SBRT for various oligoprogressive lesions in mRCC after TKI-therapy, Cheung and colleagues reported a 1-year local control of the irradiated tumors of 93% and a median PFS of 9.3 months (12). In their retrospective study on 55 patients, Santini and colleagues reported an even longer PFS of 14 months after local ablative treatment, consisting of either radiotherapy, resection or cryotherapy/thermal ablation (14). The largest study to date reports a PFS of 8.6 months after SBRT for oligoprogressive lesions after systemic therapy in 101 mRCC-patients (15).

The median OS after resection of oligoprogressive lesions in our study was 24 months. For comparison, Cheung and colleagues reported 1-year OS for SBRT with 92% and Santini and colleagues observed 37 months OS for systemic

therapy combined with various locoregional treatments in oligoprogressive mRCC (12,14). Median OS calculated from the start of systemic therapy in our study was 73 months (range, 35–135 months), whereas for mRCC treated solely with systemic therapy, Dudani and colleagues observed a much shorter median OS varying between 16 months (95% CI, 13.7–18.8 months) for pleural involvement and 25.1 months (95% CI, 24.1–26 months), when only lung metastases were present (16).

In terms of progression-free and OS, resection of oligoprogressive lesions yields encouraging results, with little morbidity. The outcome appears to be comparable to other well established local ablative measures such as SBRT. Moreover, resection of oligoprogressive lesion would offer the option of histopathological analysis and molecular sequencing which is vital to a better understanding, and ultimately, treatment of the disease.

Systemic therapy was continued directly after resection of the oligoprogressive lesions in only 3 patients and another 3 patients received systemic treatment during the further course of disease. Resection of oligoprogressive lesions can delay the need to change the initially applied systemic therapy and thus save treatment options for the future course of disease, as there are only limited lines of systemic therapies available. Furthermore, with resection, the patient can be spared side effects and the chronic toxicity of systemic therapies (12,17).

Due to the small number of patients, we could not perform any statistical analysis in our cohort to determine prognostic factors for metastasectomy for OPD in RCC. In the most recent studies, Meacci *et al.* observed in a cohort of 27 patients with isolated lung metastases, that pulmonary metastases ≥2 cm were associated with significantly shorter survival and DFI ≥5 years with significantly longer survival (18). Procházková *et al.* also reported a significant association of tumor size of the pulmonary metastases with PFS and OS in their study on 35 patients (19). Various other studies conducted between 2005 and 2017 report similar results as well as naming complete resection (R0), number of metastases and lymph node affection as prognostic factors (20-26).

As chestwall metastases are rare, only case reports have been published to date and prognostic factors have not yet been analysed in detail. Nonetheless, for bone metastases in RCC, Fottner *et al.* observed age below 65 years, absence of pathologic fractures and tumour-free resection margins to be positive prognostic factors for survival after resection (27).

Limitations

The population described in our study is heterogeneous in terms of disease burden, sites of extra-thoracic metastases and systemic treatment(s) before surgery and comprehensive treatment strategy. The studies retrospective design, in which patients were diagnosed and treated during a relatively large timeframe, hampers direct comparison of treatment and disease trajectories, as they reflect the standard of care and the guidelines at the time of treatment. Additionally, the small number of patients does not allow profound statistical analysis to draw definitive conclusions. Nonetheless, the heterogeneous settings in oligoprogressive mRCC require individual analysis to create further insight on possible advantages through radical local ablative measures and this anecdotal evidence currently provides important information on this patient collective.

Conclusions

In selected patients, resection of oligoprogressive lesions in systemically treated mRCC can lead to sustained disease control. With effective local treatment the patient can be spared toxic and chronic side effects of systemic therapy. Furthermore, treatment options for the future course of disease can be preserved. Resection of oligoprogressive lesions also offers the possibility of histopathological and molecular analysis. Reliable molecular or pathologic markers are needed for a biochemical definition of oligoprogression and identification of patients who will benefit from radical local treatment in metastasized disease.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1120/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1120/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1120/coif). The authors have no 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics board of the University of Freiburg (No. 21-1345) and individual consent for this retrospective analysis was waived.

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