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Is there a role for systemic targeted therapy after surgical treatment for metastases of renal cell carcinoma?

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Abstract

Metastatic renal cell carcinoma (mRCC) is a challenging disease. Despite the new targeted therapies, complete remissions occur only in 1%-3% of the cases, and the most effective first-line treatment drugs have reached a ceiling in overall survival (ranging from 9 to 49 mo). Metastasectomy remains to be the only curative option in most patients with mRCC. Prognostic nomograms have been recently published, so we have tools to classify patients in risk groups, allowing us to detect the cases with the higher risk of recurrence after metastasectomy. Although sparse, there is some evidence of effectiveness of neoadjuvant targeted therapy before metastasectomy; but with an increase in surgical complications due to the effects of these new drugs in tissue healing. We have aimed to answer the question: Is there a role for systemic targeted therapy after surgical treatment for metastases of renal cell carcinoma? We have made a search in Pubmed database. As far as we know, evidence is low and it's based in case reports and small series of patients treated with adjuvant drugs after neoadjuvant therapy plus metastasectomy in cases of partial response to initial systemic treatment. Despite the limitations and high risk of bias, promising results and cases with long-term survival with this approach have been described. Two ongoing clinical trials may answer the question that concerns us.

Key words: Metastatic renal cell carcinoma; Targeted therapy; Metastasectomy; Surgery; Adjuvant treatment

Core tip: We have made a search in Pubmed database looking for evidence to support adjuvant systemic therapy after metastasectomy in metastatic renal cell carcinoma. As far as we know, evidence is low and it's based in case reports and small series of patients. Despite the limitations and high risk of bias, promising results and cases with long-term survival with this approach have been described. Two ongoing clinical trials may answer the question that concerns us.

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INTRODUCTION

Renal cell carcinoma (RCC) represents 2%-3% of all cancers[1]. We know that the last two decades there has been 2% increase per year in its incidence worldwide[2].

According to largest published series, approximately 20%-30% of patients with renal cell carcinoma present metastasis at time of diagnosis. Besides, another 20%-40% of patients with localized disease who have had a surgical treatment, either partial or radical nephrectomy, will have progression during follow-up[3].

The more frequently affected organs are lungs, lymph nodes, liver and bone[4]. Nowadays, there are six targeted therapies approved for mRCC treatment. These new agents have completely changed the treatment and prognostic of patients with mRCC, but the cure is rare with medical treatment alone. Metastasectomy when feasible remains a curative option in some patients[5].

These are some of the reasons why metastatic renal cell carcinoma (mRCC) is a challenging disease. The present review aims to clarify if there is an evidence to support combination of metastasectomy and adjuvant systemic targeted therapy in mRCC.

LITERATURE STUDY

We have made a search in Pubmed database, using the key words: "renal cell carcinoma", "metastatic renal cell carcinoma", "renal cell carcinoma metastasis", "metastasectomy", "neoadjuvant treatment", "adjuvant treatment", "local treatment", "surgery"; in all languages and no date restrictions.

We included in the review all the studies that underwent the inclusion criteria: surgical treatment of metastatic renal cell carcinoma (yes/no), with emphasis on those that focused on neoadjuvant/adjuvant systemic therapy and mestastasectomy.

RESULTS

Epidemiology of mRCC treated with metastasectomy

As mentioned above, around 20%-30% of patients with RCC have metastases when diagnosed, and 20%-40% of those with localized advanced disease will progress to metastatic disease.

The most commonly affected organ in mRCC is the lungs. Lymph nodes, liver, bone, adrenal glands and brain are other typical sites; but there are reported metastases in rare organs, like pancreas, skin, bladder, *etc.*

In a recent publication, the distribution according to different organs was: 45.2% in lungs, 29.5% in bone, 21.8% in lymph nodes and 20.3% in liver. It was observed that in patients with multiple metastatic sites, 16% and 49%, brain and bone were affected, respectively[6].

Without treatment, survival of RCC is lower than 10% at 5 years[7].

Other specific characteristic of RCC is the existence of documented late metastases (> 20 years from the primary diagnosis).

The first evidence of long survival after resection of a solitary lung lesion was published in 1939[8]. Since then, several retrospective series have confirmed the effectiveness of metastasectomy. However, there are no randomized or prospective studies available.

Some authors have reported 37.2%-42% 5-year survival rates in cases of mRCC with complete resection, in observational studies[9,10].

The best response has been found in resection of solitary lung metastases, with 56% 5-year survival compared to 28% for skin, 20% for visceral organs, 18% for peripheral bone, 13% brain and 9% for axial bone metastases[11].

General prognostic factors: Knowledge of prognostic factors is important for a correct selection of patients candidates to surgery.

A retrospective study of 278 cases treated with nephrectomy and a solitary metastasis treated with surgery found that the factors associated with favourable outcome were: solitary site and single metastatasis, complete resection, a long disease-free interval and metachronous presentation[12].

In a large series of clear cell mRCC from de Mayo Clinic (Rochester, MN, United States) of 727 cases, prognostic factors of poor survival were: constitutional symptoms at nephrectomy, metastases to the bone or liver, multiple metastases, metastases at time of nephrectomy or in the 2 year thereafter, caval thrombus, Fuhrman grade 4 and coagulative tumour necrosis. In this study, complete resection of metastatic sites improved survival significantly[13].

Eggener *et al*[14] have published that in mRCC patients, the risk score classification according to Motzer classical factors and metastasectomy were independent factors of good outcome. The best survival was observed in patients with favourable risk and metastasectomy (71% 5-year survival) compared to that with high risk, with no survival at 5 years, independently of metastasectomy.

Recently, Tosco *et al*[15] have published a predictive model based on the following independent prognostic factors: primary tumour T stage $\geqslant$ 3, primary tumour Fuhrman grade $\geqslant$ 3, nonpulmonary metastases, disease-free interval $\leqslant$ 12 mo and multiorgan metastases. The Leuven-Udine (LU) prognostic groups are: (1) Group A (0-1 risk factors) with 5-year cancer specific survival (CSS) of 83.1%; (2) Group B (2 risk factors) with 5-year CSS of 56.4%; (3) Group C (3 risk factors) with 5-year CSS of 32.6%; and (4) Grupo D (4-5 risk factors) with 5-year CSS of 0%.

Another multiinstitutional study of 556 patients with mRCC who underwent metastasectomy in 48 Japanese hospitals found four adverse prognostic factors: incomplete resection of metastases, brain metastases, C-reactive protein > 1.0 mg/dL and high grade[16].

In conclusion, the prognostic factors of poor survival in patients with mRCC treated with metastasectomy are: (1) Primary tumour T stage ≥ 3; (2) Primary tumour Fuhrman grade ≥ 3 or high grade according to Japanese classification (nuclei of tumour cells larger than nuclei of normal tubular cells); (3) Nonpulmonary metastases; (4) Disease-free interval ≤ 12 mo; (5) Multiorgan metastases; (6) Incomplete resection of metastases; (7) Brain metastases; (8) C-reactive protein > 1.0 mg/dL; and (9) Motzer Classification risk score for mRCC (MSKCC risk score).

There are studies that evaluate the role of metachronous multiple metastasectomies.

In 2010, Szendröi *et al*[17] reported a case of a patient with 11-year survival after multiple and successive metastatasectomies.

In a study of 141 cases[12], 5-year survival after complete resection of second and third metastases did not differ from patients with first complete metastasectomy [43% overall survival (OS) in first resection, 46% in second and 44% in third].

In a large cohort of 887 mRCC cases, 125 underwent complete resection of multiple metastases. 5-year OS of cases with complete resection of multiple non-lung-only metastases was 32.5% compared to 12.4% of those with incomplete resection[18].

Organ-specific surgery: Lung metastases resection has demonstrated to prolong survival, with 5-year OS of 37%-55%[10,18-20].

Some prognostic factors have been described in these studies: (1) Incomplete resection has a poorer outcome (0-22% 5-year OS); (2) The presence of multiple metastases. More then 7 pulmonary metastases had worse 5-year OS (14.5% *vs* 46.8% of those with less than 7 lesions)[21]; (3) The presence of mediastinic node plus lung metastases impacted in survival (19 mo of median survival *vs* 102 mo)[22]; (4) Short disease-free interval after nephrectomy[23]; (5) Synchronous lung metastases (0% 5-year OS in patients treated with nephrectomy and metastasectomy)[24]; and (6) Size of metastases, with 0.5 cm as the established limit[25].

A prognostic model has been created based in a study of 200 cases of a single institution[26]. In multivariate analysis, size more than 3 cm, N^+ at diagnosis, pleural invasion, synchronous metastases, tumor-infiltrated hiliar, incomplete resection (R1 or R2) and mediastinal nodes were independent prognostic factors. Munich score classified patients in three groups of low, intermediate and high risk, with different median OS (90, 31 and 14 mo respectively): (1) Munich Ⅰ (low): R0, no risk factor; (2) Munich Ⅱ (intermediate): R0, ≥ risk factor; and (3) Munich Ⅲ (high): R1 or R2.

Bone metastases are often symptomatic. The indications for surgical treatment are prolongation of survival and alleviation of pain or stabilization of the extremity.

In a retrospective series of 99 cases surgically treated, the factors of good outcome were: single metastasis, wide resection and cytoreductive nephrectomy[27].

One study included a literature review, with 5-year OS of 35.8%-55%, with the best outcome in cases of peripheral skeletal location and histological subtype clear cell[28].

In a large series of M.D. Anderson Cancer Center[29] of 295 patients with 368 metastases treated, the OS rates were: 47% 1st year, 30% 2nd year and 11% 5th year. Patients with solitary metastasis showed better results, with a 5-year OS of 35%.

Patients with liver metastases have a poor prognosis due to that only 5% of the cases have a solitary metachronous lesion[30].

A series of 31 cases showed that negative resection-margin was an independent prognostic factor in multivariate analysis. The 5-year OS was 38.9%[31].

The largest retrospective series (88 patients with only liver metastases) found that those patients with synchronous metastases and a high grade RCC did not show benefit from surgery. The morbidity was 20.1%[32].

Most of the cases of brain metastases (80%) are diagnosed by symptoms. Without treatment the prognostic is poor, with a survival of less of a few months. Treatment options are surgery and stereotactic radiosurgery.

In a series of 50 cases, resection of lung metastases and supratentorial (*vs* infratentorial) localization were good prognostic factors. Adjuvant radiotherapy showed no survival advantage[33].

A series of 69 cases published in 2003, with 146 lesions treated with radiosurgery achieved good local control. OS was 6 mo from treatment. Age, neurologic status and radiosurgery dose had an impact in OS[34].

A study of 46 cases with 99 brain lesions treated with radiosurgery achieved local control in 84.7% of patients. Median OS was 10 mo, but reached 18 mo when > 75% volume decrease[35].

There have been reported 411 patients with pancreatic metastases of RCC in 170 publications[36]. Of 411 cases, 321 were surgically treated; with 65.3% of solitary lesions in surgery group. The 5-year OS was 72.6%, and disease specific survival was 57%. In-hospital mortality was 2.8%, 35.8% of patients underwent pancreaticoduodenectomy and 19.9% total pancreatectomy.

There are reports of RCC metastases in other organs, like adrenal, bladder, vagina, thyroid gland, paranasal sinuses. These publications are case reports and no clear prognosis knowledge can be made.

The panel of European Association of Urology Guidelines has made a systematic review in accordance with Cochrane review methodology[37]. They concluded that all the studies were retrospective with a high risk of bias, but with the exception of brain and possibly bone metastases, surgery remains to be by default the best treatment for most sites.

In the last actualization of the Guidelines, the conclusion is that "no general recommendations can be made and the decision of metastasectomy has to be taken for each site, and on a case-by-case basis: performance status, risk profiles, patient preference and alternative techniques must be considered".

Rationale of multimode therapy in mRCC

mRCC is a complex entity that can be treated with cytokine treatment, sequential targeted therapies and metastasectomy.

The correct moment and sequence of each treatment is not clear, but we have some evidence that combination of surgery and systemic therapies can achieved excellent outcomes.

Cytoreductive nephrectomy: It is known that nephrectomy is curative if surgery can excise all tumour deposits.

In a metaanalysis of two randomized trials comparing immunotherapy only *vs* nephrectomy and immunotherapy, a long-term survival was reported in cases treated with nephrectomy and immunotherapy in patients with good performance status[38].

In a retrospective study[39], the previous advantage of cytoreductive nephrectomy was confirmed in patients treated with vascular endothelial growth factor-targeted therapy (VEGF-targeted therapy).

However, the value of cytoreductive nephrectomy followed by VEGF-targeted therapy has to be confirmed by ongoing trials.

Adjuvant therapy after nephrectomy in localized RCC: Adjuvant tumour vaccination might improve duration of PFS in patients with T3 RCC, but has not effect in OS. Adjuvant therapy with cytokines does not improve survival[40,41].

There are several ongoing phase Ⅲ trials of adjuvant sunitinib, sorafenib, pazopanib, axitinib and everolimus.

Presurgical treatment for locally advanced RCC: Neoadjuvant treatment could be used with the following objectives: (1) Decrease tumour size and facilitate surgery; (2) Allow the performance of nephronsparing surgery; (3) Improve survival acting against micrometastases; (4) Reduce morbidity of surgery by decreasing size and vascularisation of tumour; (5) Knowledge of response to systemic therapy before surgery; and (6) Future research.

Targeted therapies have been used in neoadjuvant/preoperatory settings in cases of locally advanced RCC (huge tumours, cases with large nodes near hilium and inferior vena cava thrombus) and in cases of T2 RCC with the aim to perform a nephronsparing procedure.

Sunitinib, sorafenib, axitinib, everolimus and temsirolimus are the 5 neoadjuvant therapies that have been used for locally advanced RCC treatment and before nephronsparing surgery.

First evidence of radiological downstaging effect of kinase inhibitors was reported in phase 2 and 3 trials[42,43].

In 2009, a complete histologic remission after sunitinib neoadjuvant therapy was reported in a case of T3b renal cell carcinoma[44].

The response of renal tumours to targeted therapies has been reported in small retrospective series and case reports. The most important series are summarized in Table 1[45-54].

Powles *et al*[55] reported that in cases of mRCC treated with sunitinib prior to nephrectomy, progression prior to planned nephrectomy, high Fuhrman grade and MSKCC poor risk at diagnosis were independent prognostic factors.

Another group made a systematic review[56] and concluded that downsizing of primary tumours with neoadjuvant sunitinib or sorafenib was related to size at presentation, being the major effect in tumours sized 5 to 7 cm.

Due to the high rate of surgical complications in IVC thrombus RCC, reduction of size of tumour thrombus with neoadjuvant sunitinib, sorafenib, axitinib and temsirolimus has been reported.

The majority of the published information are case reports[57-60]. The largest series reported 25 patients, 7 of which had level 3 or 4 IVC thrombus. 12% reduced thrombus size (only after sunitinib treatment), but the reduction (Median 1.5 cm) didn't have any impact on the surgery approach[61].

In 2010, Bex *et al*[62] reported two cases of IVC thrombi progression during neoadjuvant treatment with sunitinib.

Recently, Bigot *et al*[63], in a retrospective series of 14 cases treated with sunitinib or sorafenib, found that 43% of the patients had a measurable decrease while 14% had an increase in thrombus size. Only 1 case downstaged thrombus level. However, 50% of renal tumours experienced a significant reduction in size. They concluded that neoadjuvant therapy had limited impact on IVC thrombi RCC surgical management.

In conclusion, the response of primary tumour to targeted therapies is unpredictable, although 42%-100% cases show tumour shrinkage. The major effect reported was after sunitinib treatment and in smaller tumours (5 to 7 cm). Morbidity of these novel agents should be taken into account.

There are a few studies focused on the concept of neoadjuvant systemic therapy prior to metastasectomy.

Rini *et al*[64] described 2 patients with long-term response who were treated with adjuvant sunitinib and metastasectomy.

Thomas *et al*[65] reported 19 cases treated with surgery after targeted therapy, 3 of them with metastasectomy with partial response and good outcome.

In 2009, Daliani *et al*[66] reported 38 patients with mRCC, treated with targeted therapy and a partial response/stable disease who underwent metastasectomy

Table 1 Main series of neoadjuvant therapy in locally advanced renal cell carcinoma

Ref.	No.	Therapy	Median size	% median reduction	Partial response	< 30% reduction	% cases tumour shrinkage	Toxicity Garde 3-4
Thomas *et al*[45]	19	Sunitinib	10.5	24%	3	8	42%	37%
Hellenthal *et al*[46]	20	Sunitinib	7	27.90%	2	15	85%	30%
Silberstein *et al*[47]	14	Sunitinib	7	21%	4	10	100%	3 urine leaks
Kondo *et al*[48]	9	Sunitinib/sorafenib	-	9%-30%	3	6	100%	2 major surgery complications
Rini *et al*[49]	28	Sunitinib	-	22%	-	-	-	-
Powles *et al*[50]	52	Sunitinib	-	-	-	-	73%	27%
Bex *et al*[51]	10	Sunitinib	-	14%			60%	
Kats-Ugurlu *et al*[52]	10	Sorafenib	7.5	-	-	-	-	-
Cowey *et al*[53]	30	Sorafenib	8.7	9.60%	2	23	80%	-
Karam *et al*[54]	24	Axitinib	-	28.30%	11	-	100%	41.70%

(84% only one organ site). Ten percent of patients suffered complications. Twenty-one percent of patients were remained of disease. Absence of histological viable tumour in metastasectomy specimens and lung metastases had an OS of 5.6 years compared with those who did not (1.4 years).

In 2012, Karam *et al*[67] reported 22 cases with mRCC who received neoadjuvant treatment prior to metastasectomy with one of the following targeted therapies: sunitinib, sorafenib, bavacizumab, everolimus, pazopanib, Interleukin-2, ABT-510. 4 cases had multiple mestastases and 6 suffered complications. At 109 weeks, only one patient died from RCC. 11 (50%) cases experimented no recurrence.

Another study of 2012[68], reported 11 patients treated surgically after $\geqslant$ 3 mo of stable partial remission with sunitinib, bevacizumab or sunitinib plus temisrolimus. Seven cases had node retroperitoneal disease. Only 1 complication was reported. 5 cases showed no recurrence after a median follow-up of 12 mo.

In a series of 143 patients with mRCC treated with systemic therapy, those who were treated with metastasectomy too (n = 42) had a better OS (18.8 mo *vs* 15 mo, P = 0.07)[69].

A group of Japanese authors described two cases of large adrenal mestastases with liver and pancreas invasion that were successfully treated with sunitinib prior to surgery with a good outcome[70,71].

Johannsen *et al*[72] studied the discontinuation of targeted therapy after complete response to sunitinb. 12 cases were identified, 50% (6 cases) treated with sunitinib and consolidative metastasectomy (lungs, bone, skin and thyroid). No adjuvant treatment was prescribed. Only 5 of 11 patients experienced recurrence, with effective rescue after targeted therapy in all cases. In a recent actualization of the series, with 36 cases, 33.3% remained free of recurrence during follow-up. Factors that correlate with outcome, including metastasectomy, could not be identified[73].

Adjuvant targeted therapy after metastasectomy

It is known that neoadjuvant targeted therapy can be related with surgical complications, as mentioned above. Systemic treatment can obliterate normal tissues planes and make surgery more difficult and risky[74]. A recent review concluded that no general recommendations can be made about use of targeted therapy in preoperatory setting[75].

Based on evidence of effectiveness of multimodal treatment in different moments of mRCC, we try to answer the question of the title: Is there a role for systemic targeted therapy after surgical treatment for metastases of renal cell carcinoma?

In 2007, Kwak *et al*[76] reported 93 patients with mRCC treated with metastasectomy with or without adjuvant immunotherapy. Overall survival of group treated with surgery plus immunotherapy was 56.1 mo *vs* 21.3 mo in the only-surgery group. But when patients were stratified by time of metastases, no differences were found. In multivariate analysis only multiplicity of metastases and metastases sites were independent prognostic factors. Authors concluded that metastasectomy plus adjuvant immunotherapy did not render a higher overall survival.

Jacobsohn *et al*[77] reported no effect of adjuvant Interferon after lung metastasectomy.

Since then, some case reports suggest that adjuvant targeted therapy could be effective after metastasetomy.

In 2010, a study with 88 cases with liver metastases of RCC was published. Sixty-eight were treated with surgery and 78% of cases received adjuvant treatment in both groups (metastatasectomy yes/no). The 5-year overall survival rate after metastasectomy was 62.2% with a median survival of 142 mo compared with 29.3% and 27 mo in the control group. High-grade RCC as well as patients with synchronous metastases did not benefit from surgery[32].

A case report of a man with mRCC who was treated with metastasectomy for multiple organs deposits and adjuvant pazopanib showed 8-year survival[78].

In 2012, Gardini *et al*[79] described 8 cases of pancreatic metastases of RCC treated surgically and with adjuvant therapy (mostly immunotherapy), with disease free survival after 3 years of 30%.

In most of previous papers of neoadjuvant treatment after metastasectomy, adjuvant systemic therapies

are also used. For instance, in Karam *et al*[67] study, 9 of 22 patients received at least one adjuvant targeted therapy. Effect of this intervention in survival was not assessed. Daliani *et al*[66] also gave consolidative adjuvant systemic therapy.

A study of 106 cases with mRCC and brain metastases used combination of targeted therapy and local treatments. The patients were treated with sunitinib (n = 77), sorafenib (n = 23), bevacizumab (n = 5), and temsirolimus (n = 1). Local disease treatment included whole brain radiotherapy (81%), stereotactic radiosurgery (25%), and neurosurgery (25%). On multivariable analysis, surgery or radiosurgery failed to demonstrate to increase OS[80].

Two ongoing clinical trials published in Pubmed are studying adjuvant therapy after metastasectomy: (1) RESORT protocol[81]: a randomized, open-label, multicenter phase Ⅱ study to evaluate efficacy of sorafenib in patients with mRCC after complete metastasectomy. One hundred and thirty-two patients will be randomized to receive sorafenib or best supportive care, with a follow-up of 36 mo; and (2) SMAT-AN 20/04 of the Working Group of Urological Oncology (AUO)[82]: a prospective randomized multicenter phase Ⅱ study on resection of lung metastases in clear cell carcinoma ± adjuvant sunitinib over 1 year.

CONCLUSION

mRCC is a challenging disease. Despite the new targeted therapies, complete remissions occur only in 1%-3% of the cases, and the most effective first-line treatment drugs have reached a ceiling in OS (ranging from 9 to 49 mo)[5].

Metastasectomy remains to be the only curative option in most patients with mRCC. Prognostic models for general[15,16] and lung metastases[26] have been recently published, so we have tools to classify patients in risk groups, allowing us to detect the cases with the higher risk of recurrence after metastasectomy.

Although sparse, there is some evidence of effectiveness of neoadjuvant targeted therapy before metastasectomy; but with an increase in surgical complications due to the effects of these new drugs in tissue healing.

In 2007, Jacobsohn *et al*[77] concluded that metastasectomy plus adjuvant immunotherapy did not result in a higher overall survival and published a paper titled: "No role of adjuvant therapy after complete metastasectomy in metastatic renal cell carcinoma?"

Since then, mRCC treatment has dramatically changed after the approval of new drugs. We have aimed to answer the question: Is there a role for systemic targeted therapy after surgical treatment for metastases of renal cell carcinoma? As far as we know, evidence is low and it's based in case reports and small series of patients treated with adjuvant drugs after neoadjuvant therapy plus metastasectomy in cases of partial response to initial systemic treatment. Despite the limitations and high risk of bias, promising results and cases with long-term survival with this approach have been described[32,66,67,78-80].

Two ongoing clinical trials[81,82] may answer the question that concerns us. While we wait for the results, the recommendations of European Association of Urology Guidelines[37] are a rationale tool: "the decision of metastasectomy has to be taken for each site, and on a case-by-case basis: Performance status, risk profiles, patient preference and alternative techniques must be considered". From our point of view, adjuvant targeted therapy after metastasectomy combined or not with neoadjuvant treatment could be an effective multimodal approach in the future.

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