HHS Public Access

Author manuscript

*J Urol*. Author manuscript; available in PMC 2015 December 03.

Published in final edited form as:

*J Urol*. 2011 February ; 185(2): 439–444. doi:10.1016/j.juro.2010.09.086.

# Metastasectomy Following Targeted Therapy in Patients with Advanced Renal Cell Carcinoma

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## Abstract

**Purpose—**Metastasectomy is often incorporated in the overall management of patients with metastatic renal cell carcinoma (mRCC). While this approach has been studied in the immunotherapy era, only a few cases have been described in the targeted therapy era. Therefore, we evaluated the role of metastasectomy in patients with mRCC who received prior targeted therapy.

**Patients and Methods—**Patients who underwent consolidative metastasectomy following targeted therapy at three institutions from 2004 to 2009 were evaluated in this retrospective study. All patients received at least one cycle of targeted therapy prior to surgical resection of all visible disease.

**Results—**Twenty-two patients were identified. Sites of metastasectomy included the retroperitoneum in 12 patients, lung in 6 patients, adrenal gland in 2 patients, bowel in 2 patients, and mediastinum, bone, brain, and IVC thrombus in 1 patient each. A total of 6 postoperative complications were observed in 4 patients within 12 weeks from surgery, all of which resolved with appropriate management. Postoperatively, nine patients received at least one targeted therapy. Eleven patients recurred at a median of 42 weeks from metastasectomy and another eleven patients have not experienced a recurrence at a median of 43 weeks from metastasectomy. Twenty-one patients were alive at a median follow-up of 109 weeks and one patient died of RCC 105 weeks after metastasectomy.

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**Conclusions—**In a cohort of selected patients with limited tumor burden after treatment with targeted agents, consolidative metastasectomy is feasible with acceptable morbidity. Significant time off targeted therapy and long-term tumor-free status are possible with this approach.

## Keywords

renal cell carcinoma; targeted therapy; metastasectomy

Approximately one third of patients diagnosed with renal cell carcinoma (RCC) present with metastases at initial diagnosis, and up to 40% of patients with localized RCC develop metastatic disease after radical or partial nephrectomy[1, 2]. Targeted therapy is the current standard of care for patients with metastatic RCC (mRCC), notable for higher objective responses, with improved tumor burden reduction and survival rates, compared to historical treatments [3-7]. However, complete responses to systemic therapy alone remain extremely rare.

mRCC has long been a disease where resection of metastatic deposits can be considered in the overall management of patients[8]. In general, patients who undergo metastasectomy tend to have better outcomes, independent of their risk score[9]. In the immunotherapy era, patients with a good performance status and a solitary resectable metastasis were considered good candidates for metastasectomy. Several retrospective studies investigated the use of immunotherapy prior to metastasectomy, and reported that 24-100% of patients were free of disease 1-4 years after surgery [10-15]. Kim et al[10] showed a potential benefit from integration of metastasectomy and immunotherapy, as patients treated with immunotherapy who underwent a metastasectomy had better outcomes than those who achieved an initial complete or partial response to immunotherapy, but did not undergo consolidative metastasectomy.

One study has prospectively evaluated the role of metastasectomy following immunotherapy[8]. This study included 38 patients with mRCC treated with immunotherapy with a median follow-up of 11.1 years, all of whom had either stable disease or response after therapy. All patients underwent metastasectomy and 76% achieved NED (no evidence of disease) status after surgery. In this group, the median time to progression was 1.8 years and median survival was 4.7 years; twenty-one percent of the patients remained free of disease at last follow-up.

The high response rates to targeted therapy have expanded the pool of patients potentially eligible for metastasectomy. Patients initially not considered candidates for this approach due to number, location or anatomy of metastases, may be rendered surgically resectable after a response to systemic therapy. To date, only case reports have described patients with mRCC who achieved long-term disease-free survival after treatment with sunitinib and resection of residual metastases[16]. The role of metastasectomy in patients with advanced RCC achieving NED status following response to targeted therapy has not been prospectively studied.

We report the results of a multi-institutional retrospective study to evaluate this approach in a select group of patients with mRCC who received targeted therapy followed by complete surgical resection of metastatic disease.

## Patients and Methods

This retrospective analysis included patients who underwent metastasectomy for RCC at three academic institutions (MD Anderson Cancer Center, Cleveland Clinic Foundation, and Dana Farber Cancer Institute) from October 2004 to August 2009. Appropriate Institutional Review Board approval was obtained at each center. To be included in this study, patients had to have metastatic RCC of any histologic type, and had to have received at least one cycle of targeted therapy, followed by metastasectomy aiming to resect all visible disease. The decision to perform metastasectomy was made on an individual basis, was not prospectively specified, and varied among institutions.

Patients underwent routine laboratory evaluations, and computed tomography scans of the chest, abdomen and pelvis at regular intervals according to the systemic therapy schedule while on treatment.

For analysis purposes, the retroperitoneum was considered to include any retroperitoneal nodes, periadrenal tissue, retroperitoneal musculature, or recurrence in the renal fossa. The lung was considered to include lung, pleura, or diaphragm. Clinical, pathological, and treatment-related data are presented in a descriptive fashion. Medians (with ranges) and means (with standard deviation) were used to summarize continuous variables.

## Results

### Patient demographics and disease characteristics

Twenty-two patients were included in this analysis. Demographics and baseline patient characteristics are shown in table 1. Risk stratification based on the criteria of Motzer et al [17] and Heng et al [18] is shown in table 2. All patients had a nephrectomy for RCC (21 patients had a nephrectomy prior to metastasectomy, and one patient had a nephrectomy 9 weeks after metastasectomy) and 6 patients had a prior metastasectomy, in addition to the metastasectomy of interest that followed targeted therapy. Five patients had evidence of metastases prior to nephrectomy, and 17 patients developed metastatic disease at a median of 85.3 weeks (range, 13.0-1152.3) after nephrectomy, with 11 of the 17 developing metastases one year or later after nephrectomy.

### Preoperative targeted therapy

Therapies administered prior to metastasectomy are summarized in table 3. Seventeen patients received only 1 preoperative therapy and 5 patients received two preoperative therapies each. The median duration of preoperative therapy was 45.6 weeks (range, 11.7-177.0) and the median time from last dose of preoperative therapy to metastasectomy was 27 days (range, 3-103). While on targeted therapy and prior to metastasectomy, 4 patients had a partial response, 11 patients had stable disease, and 4 patients had progressive

disease (increase in the size of index lesion without development of new metastases), per RECIST (REsponse Criteria In Solid Tumors) (information was incomplete for 3 patients)[19].

## Metastasectomy

Details about surgery-related parameters are shown in table 4. Median time from diagnosis of metastatic disease to performing the metastasectomy was 61 weeks (range, 15-259). Sites of metastasectomy included the retroperitoneum in 12 patients, lung in 6 patients, adrenal gland in 2 patients, bowel in 2 patients, and mediastinum, bone, brain, and IVC thrombus in 1 patient each. Four patients underwent metastasectomy at more than one site. At pathologic evaluation of the metastasectomy specimen, 20 patients had viable tumor while 2 patients had no evidence of tumor. These two patients did not have a preoperative biopsy of the metastases due to the location of the masses; however both had radiographic growth of the masses during observation. In addition, the masses decreased in size with targeted therapy, and pathologic evaluation of the metastasectomy specimen revealed fibrosis and/or necrosis consistent with treatment effect. One patient had a microscopic positive margin after resection of retroperitoneal metastases.

## Perioperative complications

A total of 6 postoperative complications (4 chylous ascites, 1 atrial fibrillation, and 1 ileus) were observed in 4 patients within 12 weeks from surgery, all of which resolved with appropriate management. There were no bleeding, thromboembolic, or wound complications noted within this period. One patient experienced 3 of these complications (chylous ascites, ileus and atrial fibrillation). This patient had an intraperitoneal drain placed during surgery, which was kept in place until the ascites resolved. He also received octreotide and total parenteral nutrition. The atrial fibrillation was transient, with no etiology found, and no treatment was needed. The three other patients experienced chylous ascites (1 patient had a drain placed intraperitoneally during surgery, and 2 patients required temporary percutaneous paracentesis). One patient had an intraoperative cavotomy that was repaired by primary closure with no sequelae. There were no perioperative deaths.

## Outcomes

All 22 patients were rendered tumor-free after metastasectomy. Twenty-one patients were alive at a median follow-up of 109 weeks (range, 10-283) after metastasectomy and one patient died of RCC 105 weeks after metastasectomy. Eleven patients (50%) have not experienced tumor recurrence at a median of 43 weeks from metastasectomy (range, 10-197). The other eleven patients (50%) developed tumor recurrence during the study period at a median of 42 weeks from metastasectomy (range, 6-145): three patients had both distant and local recurrences, seven patients had distant recurrences only, and one patient had local recurrence only. Ten patients had evidence of disease at last follow-up (median follow-up of 108 weeks; range, 18-283). Of note, a patient with a microscopic positive surgical margin after resection of retroperitoneal disease is currently alive at 138 weeks from metastasectomy without tumor recurrence and without postoperative therapy. There was no correlation between response by RECIST and disease recurrence.

### Postoperative targeted therapy

Postoperatively, 9 patients received at least one targeted therapy (5 sunitinib, 2 sorafenib, 2 everolimus). Eight of these patients restarted targeted therapy at disease recurrence and one patient restarted therapy 2 weeks postoperatively with no evidence of recurrence at the time. Six patients received a second postoperative targeted therapy at last follow-up (2 sunitinib + gemcitabine, 1 everolimus, 1 sorafenib, 1 pazopanib, 1 bevacizumab). Five patients received the same therapeutic agent, and four patients received a different drug postoperatively. The median time to initiate targeted therapy after metastasectomy was 55.3 weeks (range, 2-226.7).

## Discussion

To our knowledge, we report the largest experience detailing the presentation and outcomes of patients with mRCC treated in a multimodality setting with targeted therapy and metastasectomy. Twenty-one of the 22 patients were alive, and half of them were disease-free at the time of analysis. In addition, half of the patients did not receive any systemic therapy after metastasectomy. Four patients underwent surgery in the presence of 2 metastatic sites. While we typically advocate metastasectomy in the setting of solitary metastases, these patients were counseled to undergo surgery as their metastases were in close anatomical locations (amenable to surgery at the same time), and they did not experienced new metastases while on therapy. Complications were noted in 18% of the patients, but were reversible with the appropriate management, and no perioperative deaths were observed.

The use of preoperative targeted therapy in patients with advanced RCC has been retrospectively studied by several groups. Thomas et al[20] studied nineteen patients deemed to have unresectable disease who were treated with sunitinib: 11% had a partial response, 37% had stable disease and no complete responses were noted. Four patients (21%) subsequently underwent a nephrectomy, with no unexpected surgical morbidity. Margulis et al[21] compared 44 patients treated with targeted therapy prior to cytoreductive nephrectomy with a contemporary cohort of 58 patients who underwent only cytoreductive nephrectomy and did not find any significant difference in the rate of complications postoperatively (39% versus 28%, respectively, p=0.28). In contrast, Jonasch et al[22] reported a prospective phase II presurgical trial of 8 weeks of bevacizumab with or without erlotinib in 50 patients with mRCC. Bevacizumab therapy was stopped 4 weeks prior to surgery. Forty-two patients who did not demonstrate disease progression after 8 weeks of therapy underwent cytoreductive nephrectomy and had a median progression-free survival of 11 months. Two perioperative deaths occurred but were not attributable to bevacizumab-based therapy. Three patients experienced wound dehiscence, resulting in discontinuation of bevacizumab-based therapy. More recently, Cowey et al[23] conducted a prospective trial of 1 month of preoperative sorafenib in 30 patients with RCC (17 with localized disease and 13 with metastases). Of the 28 evaluable patients, 2 had a partial response and 26 had stable disease. All patients underwent cytoreductive nephrectomy as planned. Postoperatively, one patient had a myocardial infarction and another patient experienced superficial wound breakdown that was managed conservatively. No delayed wound healing, excessive bleeding or surgical

dehiscences were noted. These trials demonstrate the feasibility of pre-operative targeted therapy, but do not specifically address resection of metastatic disease.

Only a few studies have investigated the role of targeted therapy prior to resection of metastatic disease. Rini et al[16] described 2 patients who achieved tumor burden reduction with sunitinib therapy, and had subsequent metastasectomy with long-term responses. Thomas et al[24] described their experience in 19 patients who underwent 21 operations (9 had radical nephrectomy, 3 had partial nephrectomy, 6 had resection of local recurrence and 3 had metastasectomy) and experienced partial response or stable disease with targeted therapy prior to surgery. These investigators found that such approach was feasible and relatively safe. At the time of reporting, 16 patients were alive at a median follow up of 8 months, including 8 patients with disease progression. Major complications occurred in 3 patients and included death in 1 patient due to disseminated intravascular coagulation associated with partial hepatectomy, anastomotic bowel leak in 1 patient, and dialysis for 10 months in another patient. Two minor complications were also noted in patients who did not receive postoperative targeted therapy, and included a wound seroma and a ventral hernia.

In the present analysis, complications occurred exclusively in the patients who underwent retroperitoneal surgery. Caution must be exercised during these surgeries, because postoperative adhesions and anatomical distortions are typically encountered in the original field of nephrectomy. Careful hemostasis and lymphostasis are required in these particular cases to avoid the occurrence of chylous ascites. In addition, it has been reported that use of targeted therapies can obliterate normal tissue planes, rendering surgery more difficult[25]. In this small series, we did not observe any excessive bleeding or arterial or venous thromboembolic events during the study period, but investigators have to be cautioned about the increased risk of vascular complications during treatment with anti-VEGF therapies[26, 27]. A recent review extensively discussed the use of preoperative targeted therapy in a multitude of cancers and concluded that the available data are not sufficient to make general recommendations on their use in the perioperative setting. In addition, the authors called for careful use of these agents prior to surgery and for further study in a prospective fashion to further elucidate their safety profile in the presurgical setting[28].

Several questions remain unanswered in the era of targeted therapy when treating a patient with mRCC who is a potential candidate for metastasectomy, such as whether targeted therapy is needed or not, the initial choice and treatment duration with a targeted agent, and whether to resume therapy postoperatively (with the same agent or a new one) in the setting of NED. One potential advantage of treating selected patients with targeted therapy prior to metastasectomy is that this approach could act as a litmus test for patients who already have a metastasis and are at risk of developing further metastases. As such, most patients who develop metastases while on targeted therapy would no longer be eligible for surgery.

Our report has some limitations. First, although this is the largest experience investigating targeted therapy prior to metastasectomy, it is a retrospective study that included a small number of patients with a relatively short follow-up. Second, metastasectomy was performed in different organ systems and was selected on an individual basis. Third, the

type and duration of targeted therapy prior to metastasectomy were not prospectively standardized.

## Conclusion

In this report, we demonstrated that in a cohort of selected patients with limited tumor burden after treatment with targeted therapy, consolidative metastasectomy is feasible with acceptable morbidity. Metastasectomy was well tolerated, and half the patients had no evidence of disease at last follow-up. Significant time off targeted therapy and the potential for a durable remission may be achievable with this approach. A longer follow up of the current patient cohort and a prospective trial evaluating upfront targeted therapy followed by metastasectomy will be necessary before recommending this multimodality approach for the routine care of patients with mRCC.

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## Abbreviations

| | |
|---|---|
| **RCC** | renal cell carcinoma |
| **mRCC** | metastatic renal cell carcinoma |
| **NED** | no evidence of disease |

## Table 1
### Patient demographics and tumor characteristics

| Variable | Number of patients | Percentage (%) |
|---|---|---|
| **Total number of patients** | 22 | 100 |
| **Age (years)** | | |
| **Median, range** | 55.5 | 41-71 |
| **Mean, standard deviation** | 56.9 | 9.4 |
| **Gender** | | |
| **Male** | 19 | 86.4 |
| **Female** | 3 | 13.6 |
| **Race** | | |
| **White** | 17 | 77.3 |
| **Hispanic** | 3 | 13.6 |
| **Black** | 2 | 9.1 |
| **Nephrectomy** | | |
| **Right** | 11 | 50.0 |
| **Left** | 11 | 50.0 |
| **Stage at initial RCC diagnosis** | | |
| **T2** | 5 | 22.7 |
| **T3a** | 7 | 31.9 |
| **T3b** | 7 | 31.9 |
| **T4** | 1 | 4.5 |
| **Tx** | 2 | 9 |
| **Nodes at initial RCC diagnosis** | | |
| **N0** | 5 | 22.7 |
| **N1/2** | 3 | 13.6 |
| **Nx** | 14 | 63.7 |
| **Metastasis at initial RCC diagnosis** | | |
| **M0** | 8 | 36.4 |
| **M1** | 5 | 18.2 |
| **Mx** | 9 | 45.4 |
| **Histology at nephrectomy** | | |
| **Clear cell** | 15 | 68.2 |
| **Papillary** | 2 | 9.1 |
| **Chromophobe** | 2 | 9.1 |
| **Unclassified** | 2 | 9.1 |
| **Unknown** | 1 | 4.5 |

| Variable | Number of patients | Percentage (%) |
|---|---|---|
| **Fuhrman grade at nephrectomy** | | |
| **1** | 1 | 4.5 |
| **2** | 2 | 9.1 |
| **3** | 9 | 40.9 |
| **4** | 7 | 31.8 |
| **Unknown** | 3 | 13.6 |
| **Sarcomatoid elements at nephrectomy** | | |
| **Yes** | 2 | 9.1 |
| **No** | 18 | 81.8 |
| **Unknown** | 2 | 9.1 |
| **Histologic necrosis at nephrectomy** | | |
| **Yes** | 3 | 13.6 |
| **No** | 17 | 77.3 |
| **Unknown** | 2 | 9.1 |
| **History of radiation therapy** | | |
| **Yes (all brain)** | 4 | 18.2 |
| **No** | 18 | 81.8 |

## Table 2

### Patient risk classification

| | Motzer et al criteria | | Heng et al criteria | |
|---|---|---|---|---|
| **Risk Classification** | **At first systemic therapy** | **At time of metastasectomy** | **At first systemic therapy** | **At time of metastasectomy** |
| **Good** | 4 | 4 | 6 | 5 |
| **Intermediate** | 13 | 10 | 11 | 11 |
| **Poor** | 0 | 0 | 2 | 1 |
| **Missing** | 5 | 8 | 3 | 5 |

## Table 3
**Therapies received preoperatively and postoperatively**

| Therapy | Number of therapies given: | |
|---|---|---|
| | Preoperatively | Postoperatively |
| **Sunitinib** | 10 | 5 |
| **Sorafenib** | 5 | 3 |
| **Bevacizumab + interleukin-2** | 3 | 0 |
| **Sorafenib + interferon alfa** | 3 | 0 |
| **Bevacizumab** | 1 | 1 |
| **Bevacizumab + erlotinib** | 1 | 0 |
| **Bevacizumab + sunitinib** | 1 | 0 |
| **Interleukin-2** | 1 | 0 |
| **ABT-510** | 1 | 0 |
| **Foretinib** | 1 | 0 |
| **Everolimus** | 0 | 4 |
| **Sunitinib + gemcitabine** | 0 | 2 |
| **Pazopanib** | 0 | 1 |

**Table 4**

**Metastasectomy operative parameters**

| Parameter | Value |
|---|---|
| **Estimated blood loss (median, range in cc)** | 475 (0-3000) |
| **Operative duration (median, range in minutes)** | 210 (77-425) |
| **Length of hospital stay (median, range in days)** | 6 (1-17) |
| **Number of patients transfused** | 5 |
| **Size of metastasis (median, range in cm)** | 3 (1-12) |
| **Positive surgical margin** | |
| **Microscopic** | 1 |
| **Macroscopic** | 0 |
| **Intraoperative complications** | |
| **Cavotomy** | 1 |
| **Postoperative complications** | |
| **Chylous ascites** | 4 |
| **Atrial fibrillation** | 1 |
| **Ileus** | 1 |