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Primary Tumor Response to Targeted Agents in Patients with Metastatic Renal Cell Carcinoma

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Abstract

Background: The recent development of multiple targeted agents for metastatic renal cell carcinoma (mRCC) has changed the treatment paradigm; hence the benefit and optimal timing of cytoreductive nephrectomy is being reevaluated.

Objective: To determine primary tumor response to treatment with targeted agents in patients with mRCC.

Design, setting, and participants: We reviewed the clinical and radiographic data of all mRCC patients seen at our institution between November 2004 and December 2009 without prior systemic treatment who received targeted therapy with their primary tumor in situ.

Measurements: Two independent reviewers measured the diameter of primary and metastatic tumors at baseline and subsequent scans, using Response Evaluation Criteria Solid Tumors (RECIST) v.1.1 to assess disease response.

Results and limitations: We identified 168 consecutive patients with a median 15 mo of follow-up and a median maximum tumor diameter of 9.6 cm. Median maximum primary tumor response was –7.1% (interquartile range: –14.0 to –0.1).

A total of 61 patients had multiple studies available for evaluation. In 43 patients with <10% decrease in primary tumor within in the first 60 d, median maximum response was –7.2% at 154 d versus –24.5% maximum response at 174.5 d for 18 patients with ≥10% decrease in primary tumor during the initial 60 d.

Conclusions: Decrease in primary tumor diameter >30% while on targeted therapy for mRCC is rare, with most patients demonstrating minimal or no decrease in primary tumor diameter. Early response predicts a better overall primary tumor response.

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1. Introduction

The development of multiple new agents targeting vascular endothelial growth factor or cellular growth pathways has transformed the treatment of patients with metastatic renal cell carcinoma (mRCC). With its higher response rates and increased survival compared to immunotherapy, targeted therapy has become the standard first-line systemic therapy for the majority of new mRCC patients [1]. In the immunotherapy era, upfront cytoreductive nephrectomy became standard for selected mRCC patients after improved overall survival was demonstrated in two randomized trials versus interferon- α alone [2,3]. Following this accepted paradigm, the majority of patients in the initial phase 3 clinical trials of targeted agents for mRCC also underwent nephrectomy prior to receiving targeted therapy [4–9], and cytoreductive nephrectomy before systemic therapy continues to be a standard treatment for selected patients. However, the optimal timing of surgery is unknown, and the availability of improved systemic therapy has prompted a reevaluation of the role and timing of cytoreductive nephrectomy in mRCC treatment.

Recently, several groups have reported success with targeted agents in patients with the primary tumor in situ, indicating that presurgical targeted therapy may have a role in the treatment of mRCC [10–15]. However, there are no large randomized trials of presurgical targeted therapy; thus, it is difficult to know what type of response is typical and when is the best time to perform nephrectomy in a patient responding to therapy. The objective of our study was to evaluate the primary tumor response in mRCC patients treated with targeted therapy, to describe the median response, and to evaluate when this response occurs.

2. Material and methods

2.1. Patients

Upon internal review board approval, we retrospectively reviewed the medical records of all treatment-naïve mRCC patients from November 1, 2004, to December 31, 2009, who had an intact primary kidney tumor and were undergoing therapy for mRCC with targeted agents, as detailed in Table 1. The choice of targeted agent was at the discretion of the treating medical oncologist. Patients were considered eligible if images from baseline and at least one follow-up abdominal contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan were available for review. Of 212 consecutive patients identified, 27 were excluded for lack of imaging, and 17 patients were excluded because of enrollment in active clinical trials at the time of analysis. Follow-up was calculated using the Kaplan-Meier method.

2.2. Assessment of treatment response

To assess response to targeted therapy, two independent reviewers measured the diameter of primary and metastatic tumors at baseline and subsequent scans and assessed response according to Response Evaluation Criteria Solid Tumors (RECIST) v.1.1 [16]. To evaluate the response in sites other than the primary tumor, we divided the patients into two groups: patients who had clinical benefit from treatment (stable disease or partial response [PR] in metastatic sites) and patients who did not benefit from treatment (progressive disease in metastatic sites).

Pathologic data (histologic subtype, Fuhrman grade, and presence of sarcomatoid dedifferentiation) were obtained from primary tumor biopsy unless the patient had undergone subsequent cytoreductive nephrectomy, in which case data were collected from pathologic analysis of the surgical specimen.

2.3. Statistical analysis

Linear regression was used to determine the association between changes in primary tumor size and metastatic disease. Logistic regression was used to calculate an odds ratio (OR) corresponding to

Table 1 – Distribution of targeted agents, with dosage used and percentage change in primary tumor diameter while on treatment

Drug	No. (%)	Median percentage change (IQR)	Median time between imaging in days (IQR)
Sunitinib: 50 mg PO daily 4 wk on/2 wk off	75 (45)	–10.2 (–21.1 to –2.8)	105 (76–201)
Bevacizumab: 10 mg/kg IV every 14 d	25 (15)	0.1 (–4.2 to 4.6)	55 (54–56)
Bevacizumab plus erlotinib: Bevacizumab 10 mg/kg IV every 14 d + erlotinib 150 mg PO daily	26 (15)	–10.1 (–17.1 to –6.0)	54.5 (54–56)
Sorafenib: 400 mg PO twice daily	16 (10)	–6.0 (–12.3 to 0.4)	90 (61.5–124)
Temsirolimus: 25 mg IV every week	16 (10)	–4.0 (–8.6 to –0.5)	56 (52–84)
Bevacizumab plus chemotherapy: Bevacizumab 10 mg/kg IV every 14 d Gemcitabine 1200 mg/m ² IV every 2 wk Capcitabine 1.5 g twice daily for 21 of 28 d	7 (4)	–6.1 (–11.9 to –0.7)	58 (43–118)
Erlotinib: 150 mg PO daily	2 (1)	–5.1 (–9 to –1.3)	51.5 (41–62)
Pazopanib: 800 mg PO daily	1 (1)	–11.1 (–)	48 (–)

IQR = interquartile range; PO = oral; IV = intravenous.

the odds of a primary tumor response based on the radiologic response of metastatic disease sites. For all analyses, Stata v.10.1 (StataCorp, College Station, TX, USA) was used.

3. Results

We identified 168 patients (Table 2) who met the inclusion criteria for the study, with an overall median follow-up time

Table 2 – Patient and disease characteristics

Variable	Result
Age, yr, median (range; %)	59.1 (18.3–79.8; 52.8–65.1)
Tumor diameter, cm, median (range; %)	9.6 (1.8–22.1; 6.9–11.6)
Gender, No. (%)	
Male	115 (68.5)
Female	53 (31.6)
Race, No. (%)	
White	127 (75.6)
Black	16 (9.5)
Hispanic	18 (10.7)
Asian/Indian	6 (3.6)
Other	1 (0.6)
BMI, median (IQR)	27.9 (24.7–31.0)
ECOG PS, No. (%)	
0/1	123 (73.2)
2	29 (17.3)
3	16 (9.5)
Metastatic sites, No. (%)	
1	83 (49.4)
2	47 (28.0)
≥3	38 (22.6)
Side, No. (%)	
Right	68 (40.5)
Left	91 (54.2)
Bilateral	9 (5.4)
Clinical T stage, No. (%)	
T1	34 (20.2)
T2	30 (17.9)
T3a	34 (20.2)
T3b	43 (25.6)
T3c	1 (0.6)
T4	26 (15.5)
Local symptoms, No. (%)	71 (42.3)
Metastatic symptoms, No. (%)	70 (41.7)
Systemic symptoms, No. (%)	59 (35.1)
Histologic subtype, No. (%)	
Clear cell	125 (74.4)
Papillary	9 (5.4)
Chromophobe	2 (1.2)
Unclassified/other	17 (10.1)
Unknown (RCC NOS)	15 (8.9)
Sarcomatoid de-differentiation present in specimen, No. (%)	17 (10.1)
Fuhrman grade, No. (%)	
2	20 (11.9)
3	43 (25.6)
4	42 (25.0)
High grade	8 (4.8)
Unknown	55 (32.7)

BMI = body mass index; IQR = interquartile range; ECOG = Eastern Cooperative Oncology Group; PS = performance status; RCC = renal cell carcinoma; NOS = not otherwise specified.

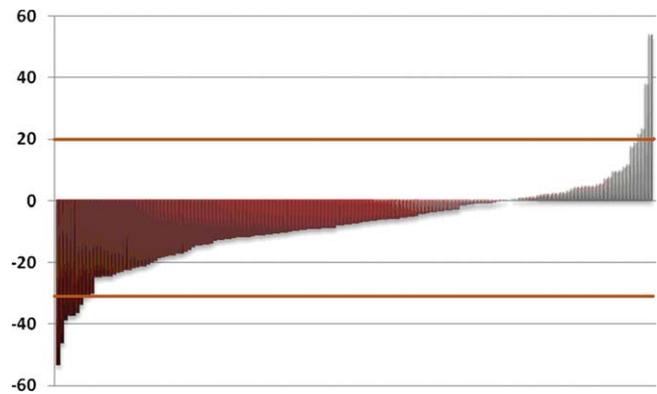


Fig. 1 – Waterfall plot showing primary tumor maximum overall response to treatment with targeted agents. Bold lines indicate partial response and progressive disease, as defined by Response Evaluation Criteria Solid Tumors.

of 15 mo (interquartile range [IQR]: 7.9–32.2). At initial evaluation, clinical rationale to defer upfront cytoreductive nephrectomy included widespread metastatic disease in 52 patients (30%), enrollment in a clinical trial in 46 patients (27%), brain metastasis, non-clear cell or sarcomatoid dedifferentiation on biopsy in 30 patients (18%), physician or patient preference in 17 patients (10%), poor performance status (PS)/comorbidities in 16 patients (10%), and primary tumor considered unresectable in 7 patients (4%).

The median maximum tumor diameter at baseline was 9.6 cm (IQR: 6.0–20.2). Median change in primary tumor size with each therapy is listed in Table 1, and the overall maximum primary tumor responses are shown in Fig. 1. The median maximum change in primary tumor diameter was –7.1% (IQR: –14.0 to –0.1) at a median time of 62 d (IQR: 54–118). The median change in primary diameter was –6.5 mm (IQR: –12.6 to –0.02). Adverse events attributed to targeted therapy are shown in Table 3, and reduction of drug dosage was required in 26 patients (16%).

When considering metastatic disease sites, 99 patients (59%) had a PR or stable disease, and 69 patients (41%) had progressive disease during treatment. Primary tumor response $\geq 10\%$ was associated with PR or stable disease in metastatic sites ($p = 0.005$). After controlling for time on therapy, patients with $\geq 10\%$ decrease in primary tumor diameter within 60 d of beginning therapy were 2.25 times more likely to have stable disease or PR to therapy (OR: 2.39; 95% confidence interval, 1.14–5.02; $p = 0.022$) in the metastatic disease sites.

Table 3 – Adverse events associated with treatment

Adverse event*	No. (%)
Fatigue	57 (34)
Stomatitis or mouth ulceration	22 (13)
Gastrointestinal complaints	15 (9)
Hypertension	11 (7)
Hand-foot syndrome	11 (7)
Hematologic events	6 (3.6)

* All complications were grade 2 or greater according to Common Terminology Criteria for Adverse Events v.4.0.

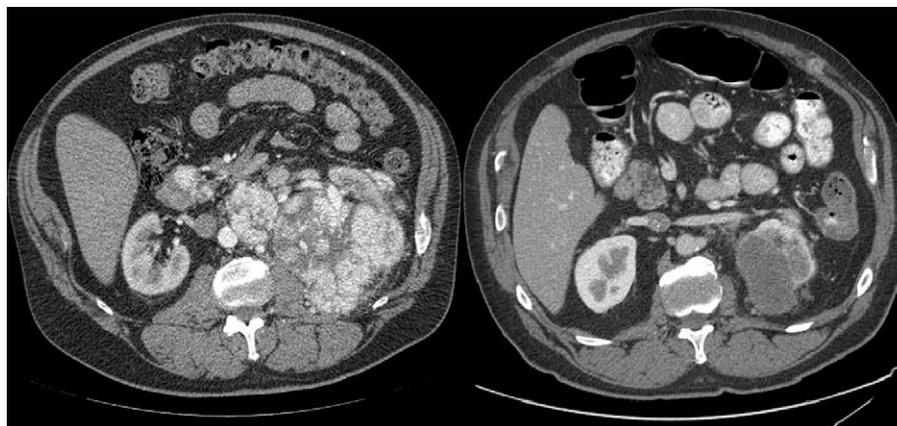


Fig. 2 – Primary tumor responding to therapy with sunitinib. Before therapy (left), the large primary tumor and lymphadenopathy would make cytoreductive nephrectomy difficult and possibly dangerous. After therapy (right), the response in the primary tumor and lymph nodes enabled this patient to undergo laparoscopic nephrectomy.

Fifty-five patients (33%) underwent delayed cytoreductive nephrectomy at a median of 75 d from treatment to surgery (IQR: 71–85). The majority of these patients received either bevacizumab ($n = 21$ [39%]) or bevacizumab and erlotinib ($n = 23$ [43%]). For patients not undergoing cytoreductive nephrectomy, a total of 23 patients (14%) continued to receive their primary targeted agent at the time of this study, the majority of whom ($n = 17$ [74%]) were treated with sunitinib. In the remaining patients, reasons for discontinuing treatment with the primary therapy included progression of disease in 64 patients (38%), unable to tolerate side effects ($n = 11$ [7%]), worsening PS ($n = 3$ [2%]), worsening comorbid conditions ($n = 5$ [3%]), surgery for metastatic disease ($n = 4$ [2%]), or an agent added as no clinical effect was seen with the original therapy ($n = 3$ [2%]).

Sixty-one patients (36%) did not undergo cytoreductive nephrectomy after the initial course of therapy or discontinued the first-line treatment because of progression. Primary targeted therapy was extended in these patients, and multiple abdominal CT or MRI studies were available for analysis (median of four imaging studies [IQR: 3–5]). Median time between treatment initiation and final imaging was 216 d, and sunitinib was the most commonly used agent (77%). The median maximum percentage change in primary tumor diameter was -11.5% (IQR: -21.8 to -4.3), which occurred at a median of 160 d (IQR: 86–225) after treatment initiation. For 43 patients (70%) with $<10\%$ reduction in the diameter of the primary tumor within the first 60 d, the median maximum response was -7.2% (IQR: -12.8 to -1.7) and occurred at a median of 154 d (IQR: 86–218). In 18 patients (30%) with $\geq 10\%$ reduction in primary tumor diameter within the first 60 d, the median maximum response was -24.5% (IQR: -36.4 to -20.7), which occurred at a median time of 174.5 d (IQR: 83–278). Among these 18 patients, 15 (83%) were treated with sunitinib, and 3 (16%) were treated with sorafenib. There was no significant difference between the times to maximum response between the two groups.

At baseline abdominal imaging evaluation, 44 patients (26%) had evidence of a tumor thrombus: 23 patients (52%)

had thrombus confined to the renal vein, and 21 patients (48%) had thrombus extending into the inferior vena cava (IVC). In two patients, the thrombus was initially within the IVC <2 cm and decreased in height to just inside the renal vein on follow-up. In another patient, the thrombus decreased from within the IVC initially just above the hepatic veins to below the hepatic veins within the IVC (>2 cm within IVC). In one patient, IVC thrombus progressed from below the hepatic veins to above the diaphragm while on therapy.

4. Discussion

Because the majority of the mRCC patients in phase 3 clinical trials with targeted agents had upfront nephrectomy [4–9], high-quality data demonstrating consistent treatment response in the primary tumor of mRCC is comparatively scarce. Recent reports have described the approach of treatment with targeted therapy prior to surgery [11–15] and have demonstrated that dramatic responses are possible (Fig. 2). In a presurgical phase 2 trial,

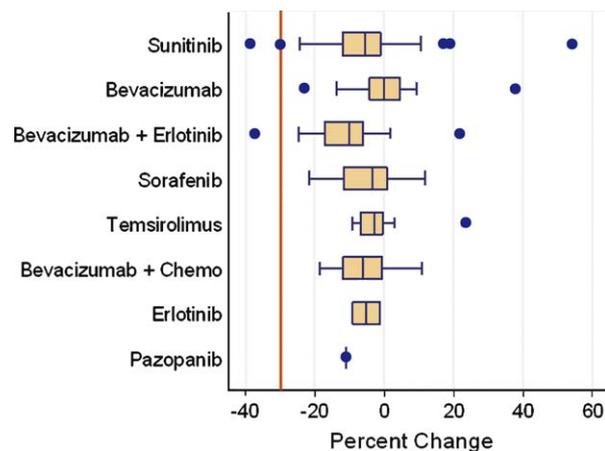


Fig. 3 – Primary tumor response to a targeted agent according to the amount of response. Most patients show minimal response or tumor stability during treatment.

Jonasch et al reported that although none of the 45 patients achieved a PR by RECIST criteria (ie, at least 30% decrease in diameter) in the primary tumor after 8 wk of bevacizumab treatment, there were 23 patients whose primary tumor diameter decreased >10% [15]. In a similar study with sorafenib, Cowey et al reported only 7% PR, but 40% of patients had >10% decrease in primary tumor size [14]. Finally, two retrospective series of 17 and 19 patients, respectively, with in situ primary tumors treated with sunitinib reported PR rates of 12% and 16%, respectively, in the primary tumor [12,13]. In the current study with 168 patients, we found a low overall rate of primary tumor PR of 6%, with >90% of patients achieving a minor response or stable disease (Fig. 3). Also, consistent with other reports, no complete responses were seen in the primary tumor.

Although even the minimal levels of primary tumor response to targeted therapy that we observed in the current study are considerably better than the reported responses with immunotherapy [17,18], primary mRCC tumors do not seem to respond as well as RCC metastatic sites. For example, sunitinib has been reported to produce objective response rates in metastatic disease as high as 37% in phase 3 clinical trials [5] compared to rates of 10–16% for the primary tumor [12,13].

Performing cytoreductive nephrectomy in patients with large tumors or advanced-stage disease is technically difficult, and resection of adjacent organs is not uncommon, with subsequent increased morbidity [19]. For these patients, the benefit of size reduction prior to surgery is obvious. However, achieving a PR is an arbitrary goal for the purposes of surgical planning, because the amount of tumor downsizing necessary to facilitate surgery is different for each patient and among surgeons. For most patients with large tumors, the 6.5-mm median decrease in diameter is not significant. However, because there is no universally accepted definition of an “unresectable” tumor, it is difficult to evaluate whether tumors become “resectable” after therapy, with the rarity of dramatic PT responses. At high-volume centers in which complex surgeries are performed by experienced surgeons, occasional responses elicited by targeted agents have intensified the debate over when to be more aggressive surgically and when to defer surgery.

With >95% of patients having stable disease or a response in their primary tumor (Fig. 3), it is rare that tumors progress and make surgery not feasible. This low level of isolated primary tumor progression has been demonstrated in prior studies [15], and early reports of surgery after targeted therapy suggest minimal or no increase in major complications using a presurgical approach [14,15,20].

RCC is known to invade vascular structures and produce venous tumor thrombi that may extend from the renal vein into the IVC and eventually into the right side of the heart, requiring complex surgery, with sternotomy and cardiopulmonary bypass in some patients. Given the apparent rarity of thrombus downstaging while on targeted therapy and risk of thrombus extension, surgical resection should remain the gold standard for the majority of patients with IVC thrombus outside of a clinical trial.

Choosing the optimal time to perform nephrectomy can be difficult in patients responding to systemic therapy. In our experience, the median time to maximum primary tumor response was between 5 and 6 mo of therapy, regardless of the amount of response. Most importantly, the response to therapy in the first 60 d was predictive of the maximum overall response. Patients with $\geq 10\%$ decrease in tumor diameter in first 60 treatment days had significantly better median overall response: 24.5% versus 7.2%. These findings are important to clinicians considering presurgical therapy in complex cases and may help guide investigators designing prospective clinical trials with presurgical therapy.

To our knowledge, the current study represents the largest series reporting primary tumor response in mRCC patients treated with targeted agents, but there are several limitations. Along with the inherent bias of a retrospective study, there is likely a selection for patients with higher-volume disease and more comorbidities compared to clinical trials with low-risk patients. However, we believe that patients with large tumors and bulky metastatic disease represent the population of patients who may benefit most from presurgical therapy. We acknowledge that the cohort of patients with multiple scans is a highly selected group for response to therapy because most patients are taken off treatment with disease progression. Nevertheless, this cohort of “responding patients” is most appropriate for evaluating the optimal timing of surgery. Finally, the criticisms of the adequacy of RECIST to assess response to targeted agents [21–23] are not relevant to our study, given that absolute size reduction is a goal in presurgical therapy.

5. Conclusions

Primary tumor response to targeted agents is highly variable (Fig. 4), with dramatic responses being rare. In the absence of evidence from randomized trials demonstrating a survival benefit for presurgical or nonsurgical treatment with targeted agents, we do not advocate changing the current paradigm of upfront cytoreductive nephrectomy prior to systemic therapy for selected patients

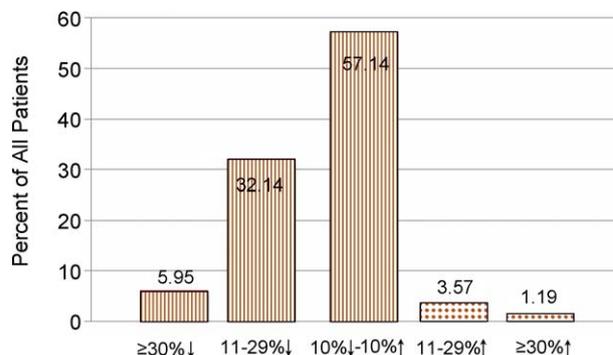


Fig. 4 – Box plot demonstrating variable primary tumor response to different targeted agents. The shaded box represents the 25th and 75th percentiles, with the ends of lines demonstrating two standard deviations and outliers shown as dots for each type of therapy.

outside of clinical trials. Presurgical therapy should be investigated in patients with unresectable, locally advanced tumors, serious comorbidities, or high-volume metastatic disease for whom upfront cytoreductive nephrectomy is rarely recommended [19,24]. Large randomized trials are in progress to answer the important questions of what is the optimal timing of cytoreductive nephrectomy and whether cytoreductive nephrectomy improves survival in mRCC patients treated with targeted agents. However, these trials are not expected to finish accrual until 2014 or 2015 [25,26], and it is critical that we evaluate current data from patients treated with the primary tumor in place to guide therapy and future research.

Author contributions: Christopher G. Wood had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Abel, Culp, Wood.

Acquisition of data: Abel, Culp.

Analysis and interpretation of data: Abel, Culp.

Drafting of the manuscript: Abel, Culp, Tannir, Matin, Tamboli, Jonasch, Wood.

Critical revision of the manuscript for important intellectual content: Abel, Culp, Tannir, Matin, Jonasch, Wood.

Statistical analysis: Abel, Culp, Wood.

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Supervision: Abel, Culp, Tannir, Matin, Tamboli, Jonasch, Wood.

Other (specify): None.

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