# Chapter 14
# Pre-surgical Treatment of Renal Cell Carcinoma


**Shivashankar Damodaran and E. Jason Abel**

## Introduction

Pre-surgical therapy is a general term referring to any treatment administered prior to surgery. In contrast, neoadjuvant therapy refers to the use of pre-surgical treatments in patients for whom surgical management may be curative. Since patients with metastatic renal cell carcinoma (RCC) are unlikely to be cured, the term pre-surgical therapy is most appropriate when discussing the treatment of patients with locally advanced or metastatic RCC.

Multiple rationales exist for the use of pre-surgical therapy in patients with RCC. These include:

- To enable surgery of unresectable tumors
- To downsize tumors such that partial nephrectomy can be performed instead of radical nephrectomy
- To facilitate minimally invasive surgery
- To decrease the extent of tumor thrombus, thereby enabling a less complex surgical approach
- To treat micrometastatic disease
- To theoretically "prime" the immune system
- To use tumor response to pre-surgical treatment as a litmus test to select patients who may benefit from surgery

S. Damodaran
Department of Urology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

E. J. Abel (✉)
Department of Urology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA
e-mail: abel@urology.wisc.edu



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Among these rationales, the use of pre-surgical therapies to reduce the size and complexity of primary tumors is perhaps the most straightforward. However, for this approach to be advantageous, pre-surgical treatments must produce substantial and reliable primary tumor responses with acceptable toxicity. For healthy patients with small localized tumors, contemporary series of nephrectomy and partial nephrectomy report minimal morbidity and mortality [1, 2]. As such, pre-surgical therapies are unlikely to improve outcomes for patients with localized tumors who can already be treated surgically with low morbidity. However, one third of RCC patients have locally advanced or metastatic disease at presentation [3], and more extensive surgery is typically required, thus increasing the risk for surgical morbidity. It is in this patient population where pre-surgical therapy has been most extensively studied.

One group of RCC patients who potentially stand to benefit from pre-surgical therapy are those with venous tumor invasion, as surgical morbidity for nephrectomy with tumor thrombectomy is considerably higher than a typical nephrectomy and morbidity substantially increases with the level of inferior vena cava (IVC) thrombus [4–6]. In a contemporary multi-institutional series of patients with RCC and IVC invasion, the perioperative mortality and major complication rate was reported to be 10% and 34%, respectively [7]. Tumors that invade directly into adjacent structures also require more extensive surgical resection including occasional removal of other organs, increasing the risk for perioperative complications. Nephrectomy for tumors invading adjacent organs is associated with substantial morbidity and poor survival in patients with positive surgical margins or metastatic disease [8–11]. Similarly, for the 15–20% of patients who present with metastatic RCC [12], cytoreductive surgery may improve survival, but patient selection remains critical [13]. Patients with metastatic RCC have a limited life expectancy [14] and a rationale for pre-surgical therapy exists if morbidity can be decreased or selection for surgery can be improved.

## Historical Pre-surgical Therapies

### *Pre-surgical Chemotherapy*

Data from phase I and phase II trials revealed early on that only a small minority of patients with metastatic RCC will be responsive to cytotoxic chemotherapy [15]. In light of this, investigations into the potential benefits of pre-surgical chemotherapy for RCC are scarce.

### *Radiation Therapy*

Preoperative radiation therapy (RT) has been investigated in patients with high-risk RCC [16–20]. In a single-center study of patients with recurrent or residual kidney cancer following nephrectomy, preoperative RT of 4.5–5.0 Gy was given followed

by aggressive surgical de-bulking and intraoperative irradiation (1.0–2.5 Gy) [16]. Four of 8 patients (50%) with clear cell RCC were free of disease at 29 months. Prospective randomized studies, however, have failed to show a survival advantage with RT in the pre-surgical setting [17–20]. More specifically, in a randomized trial of 88 patients comparing pre-surgical RT plus nephrectomy versus nephrectomy alone, 5-year survival rates of 47% and 63% were observed, respectively [18]. Similarly, in a prospective study from Rotterdam, there was no overall survival advantage to preoperative RT versus upfront surgery [19]. RT dose in this study was 30 Gy in 15 sessions and a follow-up study using a higher dose of RT showed no additional benefit [20].

## *Cytokine Therapy*

Prior to the development of modern targeted therapeutic agents, the cytokines interleukin-2 (IL-2) and interferon-α (INF-α) were commonly used for the treatment of metastatic RCC. Although effective at prolonging survival in a subset of patients with metastatic disease, these agents have been found to have little impact on the primary tumors of patients treated prior to cytoreductive nephrectomy [21–24]. Because of this, interest in the use of preoperative cytokine therapy has waned. Additionally, with the publication of two randomized phase III trials that reported improved overall survival with upfront cytoreductive nephrectomy followed by INF-α, the standard treatment sequence of upfront surgery followed by systemic therapy was established [25, 26].

### Pre-surgical Renal Artery Embolization

Selective occlusion of the renal artery prior to surgery may reduce neovascularity from large tumors or shrink tumor thrombus, potentially facilitating surgery and potentially result in less perioperative blood loss. From an immunological viewpoint, angioinfarction also releases tumor antigens stimulating a potentially beneficial immune response [27, 28]. In a retrospective analysis of 100 cases, preoperative angioembolization was found to reduce operative time and need for blood transfusion [29]. In a retrospective study that compared 118 patients matched for sex, age, stage, tumor size, and tumor grade to 116 patients who underwent surgery alone, a 5- and 10-year survival benefit was seen (62% and 47% versus 35% and 23%) [30]. However, a large series of 225 patients treated with preoperative angioembolization before radical nephrectomy and tumor thrombectomy demonstrated deleterious effects of angioembolization with increased operative time, transfusion requirements, and increased perioperative mortality [31]. Collectively, these potential risks outweigh benefits of routine angioembolization for most patients.

## Use of Targeted Therapies in the Pre-surgical Setting

Since 2005, the United States Food and Drug Administration has approved a multitude of agents for the treatment of metastatic RCC. This includes the multitarget tyrosine kinase inhibitors sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib, as well as the anti-VEGF-A antibody bevacizumab [32–37]. These agents work to slow tumor progression by inhibiting angiogenesis. Other targeted agents approved for the treatment of metastatic RCC include temsirolimus and everolimus, which are inhibitors of the mammalian target of rapamycin (mTOR) [38, 39]. Additionally the immune checkpoint inhibitor nivolumab, a monoclonal antibody targeted against programmed death receptor-1 (PD-1), was recently approved for the second-line treatment of metastatic RCC [40].

In 2008, van der Veldt et al. reported a series of 22 patients who were treated pre-surgically with the tyrosine kinase inhibitor sunitinib [41]. In 17 patients who had imaging available for response evaluation, 12 (70.6%) patients had stable disease, 4 (23.5%) had a partial response, and 1 (5.9%) had disease progression. A larger retrospective study evaluated 168 patients with metastatic RCC with the primary tumor in situ treated with targeted therapies including sunitinib, sorafenib, bevacizumab, erlotinib, pazopanib, bevacizumab + erlotinib, and bevacizumab + chemotherapy [42]. The authors found a median reduction in tumor diameter of 7.1% (interquartile range from –14% to –0.11%), with partial responses in 6% of patients.

Multiple small prospective clinical trials have been conducted to investigate the potential benefits of pre-surgical therapy in patients with RCC (summarized in Table 14.1). In a phase II trial to assess the feasibility of pre-surgical bevacizumab, 23 patients were treated with a combination of bevacizumab + erlotinib and 27 were treated with bevacizumab alone for 8 weeks [43]. Nephrectomy was performed for 42 patients (84%) and deferred for patients with disease progression or worsening performance status. Pre-surgical treatment demonstrated similar efficacy to postsurgical treatment with median overall survival of 25.4 months; however, there was a higher rate of delayed wound healing in pre-surgical treatment group.

In a phase II trial evaluating the utility of preoperative sorafenib in stage II or higher RCC, 93% of patients had stable disease, 6% patients had a partial response, and none progressed during preoperative treatment [44]. In a multicenter retrospective review to assess feasibility of sunitinib therapy prior to nephron-sparing surgery involving 14 tumors in 12 patients with clear cell RCC, 4 (35%) had a partial response and 10 (71%) had stable disease [45]. In another study aimed to evaluate safety and clinical response to sunitinib administered prior to nephrectomy, 1 (5%) patient had a partial response and 16 (80%) patients had stable disease [46]. In a combined analysis of two phase II trials to assess safety and efficacy of sunitinib prior to planned nephrectomy in patients with metastatic clear cell RCC, 5 of 52 (10%) patients achieved a partial response, while 12 (24%) had progression of disease at the time of surgery [47]. In a phase II trial of 28 patients with unresectable RCC treated with sunitinib, 7 (25%) had a partial response and 13 (45%) underwent subsequent nephrectomy [48].

**Table 14.1** Summary of primary tumor responses from clinical trials evaluating pre-surgical therapy for renal cell carcinoma

| Study | Agent | No. of patients | M1 (%) | ccRCC (%) | Median diameter reduction (%) | PR+ CR (%) |
|---|---|---|---|---|---|---|
| Jonasch et al. (2009) [43] | Bevacizumab | 50 | 100 | 100 | NR | 0 |
| Cowey et al. (2010) [44] | Sorafenib | 30 | 44 | 70 | 9.6 | 7 |
| Zhang et al. (2015) [83] | Sorafenib | 18 | 39 | 83 | 20[a] | 22 |
| Van der Veldt et al. (2008) [41] | Sunitinib | 22 | 100 | 95 | 31 | 18 |
| Silberstein et al. (2010) [45] | Sunitinib | 12 | 42 | 100 | 21[a] | 28 |
| Hellenthal et al. (2010) [46] | Sunitinib | 20 | 20 | 100 | 12[a] | 5 |
| Powles et al. (2011) [47] | Sunitinib | 66 | 100 | 100 | 12 | 6 |
| Rini et al. (2012) [48] | Sunitinib | 28 | 66 | 76 | 22 | 37 |
| Lane et al. (2015) [93] | Sunitinib | 72 | 40 | 89 | 18 | 19 |
| Rini et al. (2015) [49] | Pazopanib | 25 | 0 | 100 | 26 | 36 |
| Powles et al. (2016) [51] | Pazopanib | 104 | 100 | 100 | 14 | 13 |
| Karam et al. (2014) [50] | Axitinib | 24 | 0 | 100 | 28 | 46 |

*M1* metastatic, *PR* partial response, *CR* complete response
[a]Indicates mean reduction in diameter

Prospective phase II studies with newer generation targeted therapies have suggested slightly higher response rates in primary tumors. Pre-surgical pazopanib demonstrated partial responses in 36% of patients with localized clear cell RCC [49]. Similarly, another clinical trial evaluating pre-surgical axitinib in patients with locally advanced nonmetastatic clear cell RCC demonstrated partial responses and stable disease in 46% and 54% of patients, respectively [50]. Lower response rates were observed for patients with metastatic RCC treated with pazopanib, with only 13% of patients demonstrating a partial response with the primary tumor in situ [51].

For patients with metastatic RCC, the optimal timing of cytoreductive surgery relative to administration of targeted agents remains in question [52]. The SURTIME trial (ClinicalTrials.gov identifier NCT01099423) is an international phase III randomized study that was designed to address this question by comparing the survival of patients with metastatic RCC treated with upfront cytoreductive nephrectomy followed by sunitinib versus pre-surgical sunitinib followed by nephrectomy. This study was closed with an accrual of 99 patients with results expected to be reported in 2018. The Clinical Trial to Assess the Importance of

Nephrectomy or CARMENA trial (ClinicalTrials.gov identifier NCT00930033) is a French randomized phase III trial that will compare overall survival in patients treated with cytoreductive nephrectomy followed by sunitinib versus patients treated nonsurgically with sunitinib alone. Enrollment began in 2009 with a target accrual of 576 patients and a study completion date of 2020. Data from this trial may lend further insights into the optimal use of surgery and systemic therapy in patients with metastatic RCC.

In the future, pre-surgical administration of immune checkpoint inhibitors may have a role in the treatment of RCC, although data is still lacking for these agents. A phase I study is currently underway to analyze the safety and feasibility of preoperative nivolumab in patients with nonmetastatic stage II–IV clear cell RCC (ClinicalTrials.gov identifier NCT02575222). Results from this study are expected in 2019. Looking beyond safety and feasibility, the PROSPER trial is a phase III study designed to examine if the addition of perioperative nivolumab to radical or partial nephrectomy can prolong recurrence-free survival in patients with locally advanced RCC (ClinicalTrials.gov identifier: NCT03055013). Patients in the intervention arm of this trial will receive a combination of pre-surgical and adjuvant nivolumab. Results for this study are expected in 2022.

## Discussion of RCC Patients Most Likely to Benefit from Pre-surgical Therapy

### *Unresectable Primary Tumor*

Surgery for primary tumors that invade adjacent organs can be morbid and outcomes are poor unless negative surgical margins can be achieved [8–11]. The use of systemic therapy to facilitate surgery for unresectable tumors is a primary advantage for pre-surgical treatment and this approach has been reported by several authors [48, 53–56]. In a retrospective analysis of 19 unresectable RCC primary tumors with adjacent organ or vascular invasion treated with sunitinib, 4 (21%) were felt to have had achieved adequate cytoreduction to be deemed resectable [55]. In a similar series of tumors invading adjacent organs or in close proximity to vital structures, 3 out of 10 (33%) tumors were judged to be resectable after therapy [54]. In a phase II study involving 30 patients with unresectable RCC, 13 (45%) patients underwent nephrectomy following treatment with sunitinib [48]. Similar findings were demonstrated in a multi-institutional study of 14 unresectable patients with metastatic RCC, with 4 (28%) patients judged to be operable after targeted therapy [56].

Multiple explanations exist for the variability seen among studies using pre-surgical therapy to enable surgery in otherwise unresectable tumors. First, the definition of “unresectable” varies considerably among surgeons, and therefore conversion from unresectable to resectable is a difficult endpoint to rigorously study

in a clinical trial. In addition, truly dramatic responses to therapy are rare [42] and the choice of agent may impact outcomes [50]. Similarly, the overall disease burden may affect primary tumor response. Although there are limitations to these data, the potential benefit is considerable for pre-surgical therapy in otherwise inoperable renal tumors with invasion of adjacent organs.

## *RCC with Tumor Thrombus*

Approximately 10% of cases of RCC will present with invasion of the renal vein or inferior vena cava (IVC) [4]. The extent or level of venous invasion greatly increases surgical complexity and risk for complications [6, 7]. Thus, it stands to reason that pre-surgical therapies capable of reducing the level of a tumor thombus would decrease perioperative morbidity from tumor thrombectomy, especially if cardiopulmonary bypass is no longer necessary [57]. In several case reports, targeted therapies have produced dramatic responses in this manner, increasing enthusiasm for pre-surgical approaches in the management of locally advanced RCC [58–62]. However, the responses that were demonstrated in cases reports were not reproduced in larger series [63, 64]. More specifically, a study of 25 patients with level 2 or higher IVC tumor thrombi treated with pre-surgical targeted therapy demonstrated that dramatic responses are rare [64]. Height, diameter, and level of thrombus were measured radiographically and used as endpoints for the study. Patients were treated with sunitinib ($n = 12$), bevacizumab ($n = 9$), temsirolimus ($n = 3$), and sorafenib ($n = 1$). Only three patients (12%) had a decrease in thrombus level, while 1 (4%) patient had an increase in thrombus level, and 21 (84%) did not have any change in the thrombus level. None of the patients had a modification of surgical approach as a result of the response to the targeted therapy.

Bigot et al. [63] reported another retrospective series of 14 patients with tumor thrombus who were treated with pre-surgical sunitinib or sorafenib. After therapy, six patients (43%) had a measurable decrease in the thrombus size, six (42%) had no change in size, and two cases (14%) progressed. The authors concluded that preoperative use of tyrosine kinase inhibitors produced a minimal reduction in the thrombus size, which did not modify subsequent surgical therapy. Kwon et al. [65], however, did find slightly more encouraging results in a retrospective study of patients with RCC and thrombus treated with pre-surgical targeted therapy. In their cohort of 22 patients, 18 (82%) received sunitinib and 4 (18%) received sorafenib as neoadjuvant targeted therapy. The authors used the Choi criteria [66] to evaluate tumor response, which defines partial response as >10% decrease in one-dimensional tumor size or >15% decrease in the maximal attenuation on X-ray computed tomography (CT). Nine patients (40.9%) demonstrated a partial response and had a longer survival than patients who had stable disease. In a multivariate analysis, response by the Choi criteria was the only significant predictor of overall survival.

Given that rarity of responses in tumor thrombus well as the risk of progression during therapy [67], pre-surgical treatment with currently available agents is

unlikely to benefit otherwise healthy patients without metastatic disease. However, certain patients with metastatic RCC and tumor thrombus may have very poor expectations for overall survival despite treatment with upfront nephrectomy and systemic therapy. In a multi-institutional study that looked at overall survival in metastatic RCC with venous tumor thrombus treated with cytoreductive nephrectomy, IVC thrombus above the diaphragm, poor risk group, systemic symptoms, and sarcomatoid dedifferentiation were associated with poor overall survival [68]. Patients with very limited life expectancy may benefit from pre-surgical clinical trials if the benefit of future systemic agents outweighs the risk of deferring surgery.

## *Metastatic Renal Cell Carcinoma*

The prognosis of patients with metastatic RCC remains poor, with a median overall survival of slightly less than 2 years [69, 70]. Although upfront cytoreductive nephrectomy remains part of the standard treatment paradigm, the selection of patients for surgery is critical [71]. Contemporary population-based studies have estimated that only 36–46% of patients with metastatic RCC are treated with cytoreductive nephrectomy [72, 73]. Clinical and pathological variables [13] as well as prognostic risk stratification tools [74] are currently used to identify patients who are most likely to benefit from cytoreductive nephrectomy. Response to systemic therapy, however, may also enable selection of patients, providing a "litmus test" for patients likely to benefit cytoreductive nephrectomy [43, 75].

Survival from metastatic RCC is exceptionally variable and a subset of patients will rapidly progress despite maximum therapy [14, 76]. Proponents of upfront systemic therapy for metastatic RCC argue that patient selection for surgery will be improved if therapeutic response is used as a selection criterion for cytoreductive nephrectomy [52]. Using this approach, surgery can be avoided in the subset of patients who progress and quickly succumb to their disease despite targeted therapy. Disease prognosis could then be estimated based on initial treatment response. Of note, Heng et al. [77] found in an analysis of 1056 patients treated with anti-VEGF agents for RCC that 26% of patients had progressive disease as their best response to therapy. The median overall survival of these patients was 6.8 months compared to 29 months in patients who had either stable disease or responded to systemic therapy. Importantly, the poor overall survival in this subset was not predicted by known risk stratification systems, with only 39% of patients being considered poor risk by the widely used International Metastatic Renal Cell Carcinoma Database Criteria.

The potential for selecting patients for cytoreductive nephrectomy based on response to upfront systemic therapy was demonstrated in a phase II clinical trial of patients with metastatic RCC treated with upfront bevacizumab prior to surgery [43]. Of the 50 patients in the final analysis, 42 (84%) were treated with cytoreductive surgery after restaging following 8 weeks of systemic therapy and 8 patients did not undergo cytoreductive nephrectomy, with 6 (12%) patients showing clinical or

radiographic progression. In another study of 75 patients with metastatic RCC who were treated with sunitinib with the primary tumor in situ, it was found that patients who had a ≥10% response in their primary tumor within the first 60 days of treatment had a median overall survival of 30 months as compared to 16 months for less favorable responders [75]. In a single-arm phase II trial involving 104 metastatic RCC patients treated with 12–14 weeks of pre-surgical pazopanib therapy, 63 (61%) patients underwent subsequent nephrectomy and 13 patients progressed on pazopanib therapy. These patients had poor overall and progression-free survival implying pre-surgical systemic therapy can be used as a litmus test for choosing patients for subsequent surgery.

## *Enabling Partial Nephrectomy for Complex Tumors*

For patients with small renal tumors, partial nephrectomy is the preferred treatment option because of the importance of preserving renal function [78, 79]. Thus, there is a potential benefit for pre-surgical therapy if treatment increases the feasibility of partial nephrectomy by shrinking tumors and enabling nephron preservation. This benefit can be potentially most impactful in patients who have a solitary functioning kidney.

In a multicenter retrospective analysis of 12 patients with 14 biopsy proven clear cell RCCs who were preoperatively treated with sunitinib, the authors observed that all tumors had a decrease in size, with a mean reduction in maximum diameter of 1.5 cm (21.1%) [45]. Additionally, nephron-sparing surgery was achievable in all 14 kidneys. In a phase II trial of nonmetastatic RCC patients treated with preoperative axitinib, Karam et al. observed partial responses in 11 (46%) patients with a median reduction in tumor diameter of 28% [50]. The authors subsequently performed a retrospective analysis of data from this trial in which five urological surgeons were independently surveyed as to whether pre-surgical systemic treatment facilitated performance of partial nephrectomy [80]. The authors observed a decrease in the median R.E.N.A.L. nephrometry score from 11 to 10 following treatment with axitinib. In addition, all five reviewers agreed that only five patients required treatment with a radical nephrectomy following treatment. In comparison, the five reviewers felt that eight patients required a radical nephrectomy prior to treatment, suggesting a change in surgical approach to partial nephrectomy was possible in a subset of patients.

## *Enabling Minimally Invasive Surgery*

Reducing morbidity by utilizing minimally invasive approaches is another possibility for patients following pre-surgical therapy. However, like unresectable tumors, the ability to perform minimally invasive approaches is a poor endpoint for clinical trials since this definition varies widely among surgeons [81]. As such, the ability to

facilitate minimally invasive surgery has not been studied as a primary endpoint and few data are available to analyze. In the phase II trial of pre-surgical axitinib for patients with T2–T3b tumors, 5 out of 24 (21%) had minimally invasive surgery following treatment [50]. If reliable and dramatic responses are demonstrated with newer systemic agents, this approach may be studied further as a method to decease perioperative morbidity.

## Safety of Pre-surgical Targeted Therapy

Since many targeted therapies also inhibit pathways that are involved in wound healing, the safety of pre-surgical therapy remains a concern. An early clinical trial evaluating pre-surgical treatment with bevacizumab in patients with colorectal cancer reported higher complication rates with pre-surgical treatment [82]. Similarly, a pre-surgical study of bevacizumab in patients with metastatic RCC demonstrated higher rates of wound dehiscence and delayed wound healing compared to historical controls (20.9% versus 2%; $p < 0.001$) [43]. However, data with tyrosine kinase inhibitors appears to be more favorable. For example, patients treated with sorafenib have not shown associated complications with delayed wound healing, dehiscence, or excessive bleeding [83]. Likewise, a pre-surgical clinical trial with axitinib reported only one patient (4.2%) with a superficial wound healing complication [50]. In a study of 173 patients with metastatic RCC comparing pre-surgical systemic treatment to upfront cytoreductive surgery, 90 days complication rate, multiple complications, and wound complications were higher, but major complication rates (≥Clavien 3) were not increased with pre-surgical therapy [84]. Many of the patients with wound complications were treated with pre-surgical bevacizumab, which has a significantly longer half- life (17 days) as compared to sunitinib (4 days) [85] and pazopanib (31 h) [86]. Current recommendations are to discontinue bevacizumab for 30 days prior to surgery and not restart for at least 30 days postoperatively [87].

## Duration of Therapy

The optimal duration of pre-surgical treatment is unknown but depends on several factors including the rationale for treatment and strength of response to an individual agent. In order to shrink tumors to facilitate surgery, pre-surgical treatment should maximize responses in the shortest possible time. Tumors that respond to pre-surgical therapy undergo extensive vascular remodeling that decreases tumor size, which generally has been observed within the first two cycles of therapy [88]. The median duration of therapy in contemporary studies of sunitinib was two cycles, with each cycle including 4 weeks of therapy with 50 mg daily followed by 2 weeks off [89, 90]. The duration of sorafenib therapy ranged from 33 to 96 days, and for

pazopanib it was from 8 to 14 weeks [90]. Therefore, a short course of therapy with radiological monitoring of tumor response is critical for timing of surgery following pre-surgical therapy. After treatment, patients should be scheduled for surgery as soon as possible because the risk of rapid tumor regrowth and progression after stopping therapy [91, 92].

## Conclusions

Although there are no large randomized clinical trials demonstrating benefit of pre-surgical therapy for patients with RCC, there is a potential for benefit in well-selected patients treated with targeted agents. Large complex tumors that are judged to be unresectable may shrink during pre-surgical treatment and facilitate surgery. Additionally, response to pre-surgical therapy may facilitate nephron-sparing surgery or conversion from an open to minimally invasive surgical approach. Likewise, patients with metastatic RCC may benefit from upfront systemic therapy as a litmus test to judge the potential benefit from cytoreductive nephrectomy. Most studies with pre-surgical targeted agents have demonstrated the safety of this approach, with slightly increased risk for wound complications. However, dramatic responses are uncommon, and the possibility of progression while on therapy must be considered. Clinical use of pre-surgical therapy should continue to be investigated especially in RCC patients who have the strongest rationale for treatment including unresectable primary tumors and metastatic disease. Ultimately, additional clinical trials are needed in this arena.

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