Does timing of targeted therapy for metastatic renal cell carcinoma impact treatment toxicity and surgical complications? A comparison of primary and adjuvant approaches

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Introduction: *To compare surgical complications and tyrosine kinase inhibitor (TKI)-toxicities in patients who underwent primary cytoreductive nephrectomy (CN) followed by adjuvant TKI therapy versus those who underwent neoadjuvant TKI therapy prior to planned CN for metastatic renal cell carcinoma (mRCC).*

Materials and methods: *Two-center retrospective analysis. Sixty-one mRCC patients underwent TKI therapy with sunitinib between July 2007 to January 2014. Patients were divided into three groups: primary CN followed by adjuvant TKI (n = 27, Group 1), neoadjuvant TKI prior to CN (n = 21, Group 2), and primary TKI alone (no surgery, n = 13, Group 3). Primary outcome was frequency and severity of surgical complications (Clavien). Secondary outcome was frequency and severity of TKI-related toxicities (NIH Common Toxicity Criteria). Multivariable analysis was carried out for factors associated with complications.*

Results: *There were no significant differences in demographics, ECOG status, and median number TKI cycles (p = 0.337). Mean tumor size (cm) was larger in Group 3 (12.8) than Group 2 (8.9) and Group 1 (9.3), p = 0.014. TKI-related toxicities occurred in 100%, 90.5%, and 88.9% in Group 3, Group 2, and Group 1 (p = 0.469). There was no difference in incidence of high grade (p = 0.967) and low grade (p = 0.380) TKI-toxicities. Overall surgical complication rate was similar between Group 2 (47.6%) and Group 1 (33.3%), p = 0.380. Group 2 had more high grade surgical complications (28.6%) than Group 1 (0%), p = 0.004. Multivariable analysis demonstrated increasing age was independently associated with development of surgical complications (HR 1.059, p = 0.040).*

Conclusion: *Patients receiving neoadjuvant TKI therapy prior to CN experienced more high grade surgical complications than patients who underwent primary CN. Potential for increased high grade surgical complications requires further investigation and may impact pretreatment counseling.*

Key Words: carcinoma, renal cell, clavien, metastasis, neoadjuvant therapy, nephrectomy, sunitinib, tyrosine kinase inhibitor, surgical complications, toxicity

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Introduction

In 2016, 62,700 cases of renal cell carcinoma (RCC) are estimated to occur in the United States[1] with up

to 30% presenting with metastatic disease (mRCC).[2] Targeted therapy with tyrosine kinase inhibitors (TKIs) has shown to achieve a median overall survival > 2 years in patients with metastatic renal cell carcinoma (mRCC),[3] establishing TKIs as first-line therapy. In the era of immunotherapy, randomized controlled trials demonstrated survival benefit for cytoreductive nephrectomy (CN) with immunotherapy versus immunotherapy alone.[4,5] The role of CN in the TKI era remains controversial in the absence of level-one evidence. Most level-one evidence supporting targeted therapy is in the presence of CN,[3] and large retrospective comparative analyses demonstrate improved outcomes in patients who undergo CN and systemic TKI therapy versus those who undergo systemic targeted therapy alone.[6] Emerging reports suggest that primary TKI may serve as a biological litmus test to avoid major operative intervention in patients who may not benefit from such an intervention. These reports also suggest that outcomes are improved when TKI is followed by CN, compared to patients who receive systemic therapy after CN.[7,8] The impact of neoadjuvant TKI on surgical complications, as well as subsequent medical side effects and sequelae is unclear.[9] Prior studies have demonstrated similar rate of perioperative complications, including significant (Clavien ≥ 3) complications.[7,9] However, most studies have had either heterogeneous cohorts with respect to agents or have been small series. Furthermore, the impact of surgical intervention on toxicity profile of targeted therapy is unclear. We examined the impact of neoadjuvant TKI therapy on surgical complications in patients undergoing CN for mRCC and evaluated impact of timing of CN on TKI-related toxicities

Materials and methods

Study patients

Investigational Review Board-approved (UC San Diego Health System; University of Tennessee Health Sciences Center, Memphis) retrospective analysis of patients diagnosed with mRCC from July 2007 to January 2014 who were considered at the time of initial evaluation for CN. Our evaluation, treatment and operative protocols have been described previously.[8,10,11] All patients included in this analysis were offered primary systemic therapy. We excluded 9 patients with an overwhelming burden of metastatic disease, with poor performance status, who proceeded to systemic therapy after the initial evaluation without a plan to offer CRN. Patients were also excluded if tumor histology was not clear cell RCC (n = 5), if they had undergone prior chemotherapy or immunotherapy (n = 3), or those in whom the primary targeted treatment was other than sunitinib (n = 6), or with < 3 months follow up with no clear evidence of death or progression within that period (n = 2). Of the 61 patients included in the study, 27 underwent primary CN, followed by sunitinib (Group 1), 21 underwent primary or neoadjuvant sunitinib therapy before intended CN (Group 2), and 13 underwent primary TKI therapy alone (Group 3, no CN, n = 13).

Patients underwent complete staging chest, abdominal, and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), and when appropriate, brain imaging and bone scintigraphy. Percutaneous renal or metastasis biopsy to confirm clear cell RCC was completed in all patients before systemic therapy was initiated. American Joint Committee on Cancer 2010 classification was used to assess TNM stage, and pathology/Fuhrman grade was determined according to 2004 World Health Organization criteria.[12,13] Performance status was evaluated according to Eastern Cooperative Oncology Group (ECOG) criteria.[14]

Treatment and assessment of response

Sunitinib (Sutent, Pfizer, New York, NY, USA) was used as the first-line targeted agent, with failures going on to secondary/salvage systemic therapy. Sunitinib was administered orally at 50 mg once daily for 6 week cycles consisting of 4 weeks of treatment, followed by 2 weeks without treatment. The standard dose was modified in 12.5 mg steps (50 to 37.5 to 25.0) based on individual safety and tolerability.[8,11] In patients receiving adjuvant TKI after CN, sunitinib was started 4 weeks after CN. Cycles were continued according to patient tolerability or until there was a failure to respond to therapy. In that case, second- and third-line agents (sorafenib, temsirolimus, bevacizumab) were administered. In patients receiving neoadjuvant TKI before CN (Group 2), sunitinib was administered for 2 cycles before planned CN, followed by assessment of response. These patients who had partial response or stable disease proceeded to CN after a 2 week washout period. Sunitinib was resumed 4 weeks postoperatively, depending on the presence of residual disease. Group 2 patients who progressed were not offered CN and were treated with salvage systemic therapy (Group 3).

Tumor response to therapy was assessed by CT/MRI after every 2 to 3 cycles of treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[15] Clinical response of primary tumor and metastatic sites was classified by treating physicians as complete response (CR), partial response

(PR), stable disease (SD), and progressive disease (PD). We defined responders as those with a PR or SD, and nonresponders were those with PD.

Primary outcome was rate of high grade surgical complications, and secondary outcome was rate and TKI-related toxicities. The Clavien classification system was used to characterize complications after surgery; grade III-V complications were considered high grade.[16] TKI toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[17]

Data and statistical analysis

Patient demographics, clinical variables, perioperative outcomes and toxicity/complications were compared between groups. Tests performed included the independent t-test, analysis of variance, Mann-Whitney U test, and Kruskal-Wallace tests for continuous variables (dependent on distribution), and Chi-square and Fisher exact tests for categorical values. Multivariable analysis conducted to analyze factors associated with development of surgical complications and TKI toxicities. Statistical analysis was performed using SPSS 17 software (SPSS Inc, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

Patient demographic and clinical characteristics are summarized in Table 1. Baseline characteristics between the Groups were similar with a median follow up from first treatment of 11.6 months for Group 3, 42.5 months for Group 2, and 28.1 months for Group 1, p = 0.337. Mean clinical tumor size was significantly larger in Group 3 (12.8 cm) compared to Group 2 (8.9 cm) and Group 1 (9.3 cm), p = 0.014. Patients in Group 3 had a higher presence of inferior vena cava thrombus, p = 0.026. The median number of sunitinib cycles was similar between the groups (Group 3, 2 cycles; Group 2, 2 cycles; and Group 1, 2.4 cycles, p = 0.337). Group 2

TABLE 1. **Demographics and clinical characteristics**

	Group 1 (n = 27)	**Group 2 (n = 21)**	**Group 3 (n = 13)**	**p value**
Demographics				
Mean age ± SD, years	59 ± 14.9	57 ± 12.5	53 ± 9.8	0.423
Gender				0.752
Male	17 (63.0%)	14 (66.7%)	7 (53.8%)	
Female	10 (37.0%)	7 (33.3%)	6 (46.2%)	
Race				0.113
Caucasian	19 (70.4%)	8 (40.0%)	7 (53.8%)	
Other	8 (29.6%)	12 (60.0%)	6 (46.2%)	
Mean BMI ± SD, kg/m^2	27.2 ± 4.5	29.1 ± 4.8	27.4 ± 7.0	0.453
ECOG performance status				0.173
0-1	19 (70.4%)	19 (90.5%)	8 (66.7%)	
> 1	8 (29.6%)	2 (9.5%)	4 (33.3%)	
Clinical characteristics				
Mean clinical tumor size ± SD, cm	9.3 ± 2.9	8.9 ± 4.8	12.8 ± 3.4	0.014
IVC thrombus	7 (25.9%)	7 (33.3%)	9 (69.2%)	0.026
Number of metastases				0.091
1-5	13 (61.9%)	15 (88.2%)	7 (53.8%)	
> 5	8 (38.1%)	2 (11.8%)	6 (46.2%)	
Median months from surgery to TKI initiation (IQR)	1.4 (0.9-2.4)	-	-	-
Median months from TKI initiation to surgery (IQR)	-	3.8 (3.1-6.0)	-	-
Median number of TKI cycles (IQR)	2.4 (2.0-10.0)	2.0 (2.0-3.0)	2.0 (2.0-10.5)	0.843
Median follow up from first treatment (IQR), months	28.1 (11.8-36.9)	42.5 (8.7-61.0)	11.6 (7.3-14.1)	0.337

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; IVC = inferior vena caval; TKI = tyrosine kinase inhibitor

TABLE 2. **Perioperative variables and surgical complications**

	Group 1 (n = 27)	Group 2 (n = 21)	p value
Nephrectomy type			0.001
Radical	26 (96.3%)	12 (57.1%)	
Partial	1 (37%)	9 (42.9%)	
Surgical approach			0.776
Open	14 (51.8%)	13 (61.9%)	
Minimally invasive	13 (48.1%)	8 (38.1%)	
Mean operative time ± SD, minutes	230 ± 67	240 ± 60	0.706
Median estimated blood loss (IQR), mL	500 (200-750)	500 (250-825)	0.558
Median hospital length of stay (IQR), days	4.5 (3-8)	7 (5-11)	0.034
Surgical complications	9 (33.3%)	10 (47.6%)	0.380
Low grade 1/2	9 (33.3%)	6 (26.8%)	0.764
High grade 3a/b	0	6 (26.8%)	0.004
Bowel leak	0	1 (4.8%)	0.438
Fluid collection	0	1 (4.8%)	0.438
Hernia	0	1 (4.8%)	0.438
Urine leak	0	3 (14.6%)	0.077

had a median of 3.8 months from time of TKI treatment to surgery, while the Group 1 had a median of 1.4 months from surgery to TKI initiation.

Table 2 summarizes perioperative parameters and surgical complications. A higher proportion of patients in Group 2 underwent partial nephrectomy than in Group 1 (42.9% versus 3.7%, p = 0.001). Partial nephrectomy was performed for imperative indications in all patients who underwent the procedure (5 patients had solitary kidney, 4 had bilateral tumors, and 7 patients had baseline chronic kidney disease). There were no differences between the two groups with respect to: surgical approach (Group 1 open 51.8% versus Group 2 open 61.9%, p = 0.776), mean operative time (Group 1 230 ± 67 minutes versus Group 2 240 ± 60 minutes, p = 0.706) and median estimated blood loss (both groups 500 mL, p = 0.558). Median hospital length of stay was significantly longer in Group 2 (7 days, IQR 5-11) than Group 1 (4.5 days, IQR 3-8), p = 0.034. The overall surgical complication rate was similar between Group 2 (47.6%) and Group 1 (33.3%), p = 0.380. A similar rate of low grade complications (Clavien 1/2) was noted between Group 2 and Group 1, 26.8% versus 33.3%, p = 0.764. However, Group 2 had a significantly higher rate of high grade (Clavien 3/4) surgical complications (28.6%) compared to Group 1 (0%), p = 0.004. High grade complications in the Group 2 included 3 patients with urine leaks after partial CN (all were managed with percutaneous drainage with successful resolution), 1 patient with a recognized enterotomy and repair at time of radical CN, which was complicated by postoperative bowel leak requiring re-exploration, 1 patient with fluid collection and 1 patient with postoperative hernia requiring re-operation/repair. To adjust for the prevalence of urine leaks after partial CN, a subanalysis was performed to examine patients who underwent only cytoreductive radical nephrectomy only. This subanalysis, overall surgical complication rate was similar for Group 2 and Group 1 (50% versus 30.8%, p = 0.296), low grade complications were similar (p = 1.000) and a significantly higher rate of high grade complications was still noted in Group 2 (25%) versus Group 1 0%, p = 0.026).

TKI-related toxicities are summarized in Table 3. Overall TKI-related toxicities were 100%, 90.5%, and 88.9% in Group 3, Group 2, and Group 1, p = 0.469. There was no difference between the three groups in regard to low grade (100% versus 85.7% versus 88.9%, p = 0.380) and high grade (38.5% versus 35% versus 38.5%, p = 0.967) TKI-related toxicities.

Multivariable analysis demonstrated that increasing age was the only variable associated with development of surgical complications (HR 1.059, p= 0.040). Variables entered into the model included treatment group, age, race, BMI, ECOG PS, type of procedure performed, surgical approach, RENAL nephrometry score, tumor grade, and presence of thrombus. Multivariable analysis carried out for factors associated with development of TKI-related toxicities did not

TABLE 3. **TKI toxicities**

	Group 1 (n = 27)	Group 2 (n = 21)	Group 3 (n = 13)	p value
TKI toxicities	24 (88.9%)	19 (90.5%)	13 (100.0%)	0.469
Low grade 1/2	24 (88.9%)	18 (85.7%)	13 (100.0%)	0.380
High grade 3/4	10 (38.5%)	7 (35.0%)	5 (38.5%)	0.967
Decreased potassium	0	2 (9.5%)	0	0.140
CVA	0	0	1 (7.7%)	0.153
Fatigue	0	1 (4.8%)	0	0.380
Lower extremity edema	0	0	1 (7.7%)	0.153
Hypertension	7 (26.9%)	3 (14.3%)	4 (30.8%)	0.461
Mucositis	1 (3.7%)	0	0	0.537
Hand/foot syndrome	2 (7.4%)	0	0	0.282
Peri-rectal abscess	0	1 (4.8%)	0	0.380
Scalp itch	1 (3.7%)	0	0	0.527

TKI = tyrosine kinase inhibitor

yield independent factors. Variables entered into the model included treatment group, age, race, BMI, ECOG PS, surgical treatment approach, RENAL score, tumor grade, presence of thrombus, and number of TKI cycles.

Discussion

With improved response rates and outcomes ushered in by targeted therapies for mRCC, questions have been raised about the impact and necessity of CN as well as the potential effect of CN on systemic treatment. With the development of targeted therapies, a new treatment paradigm of neoadjuvant therapy prior to CN has emerged, with suggested benefit with respect to improved disease specific and overall survival compared to patients who undergo primary CN prior to systemic treatment.[6-8] However, in this setting, questions remain regarding the safety profile, timing of treatment and expectations in postoperative complications.

Our analysis demonstrates that patients who underwent neoadjuvant therapy (Group 2) had a significantly higher high grade surgical complication rate (28%) than patients who underwent primary CN (Group 1, 0%, p = 0.004); furthermore, rates of overall (p = 0.469) and severe treatment related toxicity (p = 0.380) were not significantly different between primary CN, neoadjuvant TKI followed by CN, and TKI alone groups. Our findings are different from other recent reports which suggest no significant difference in surgical complication rates. Harshman et al analyzed 14 cytoreductive nephrectomies, radical nephrectomies, and metastectomies performed after neoadjuvant sunitinib (n = 10) or sorafenib (n = 4) for advanced RCC with a control group of 73 patients who underwent radical nephrectomy, cytoreductive nephrectomy, or metastectomy in the absence of prior systemic therapy.[9] They noted that presurgical TKI use was not associated with a significant increase in perioperative complications (50% versus 40%, p = 0.25) but was associated with increased incidence and grade of intraoperative adhesions (86% versus 58%, p = 0.001). While the majority of their neoadjuvant cohort (12/14 = 85.7%) had metastatic disease, 30.7% (23/75) of their non-neoadjuvant cohort had metastatic disease; therefore the heterogeneity of the comparator cohorts (with the inclusion of a substantially greater proportion of nephrectomy for non mRCC, which may carry a lower risk of blood loss and complications)[18-19] and the small size of the neoadjuvant cohort in this study, may have therefore produced a comparison which was underpowered to detect significant difference between the neoadjuvant and primary nephrectomy groups. Margulis et al analyzed perioperative complications in 44 patients treated with targeted therapies, and prior to surgery (CN or resection of local RCC recurrence) and 58 patients who underwent up-front surgery prior to targeted therapy, and noted that 17 (39%) of patients treated with preoperative targeted and in 16 (28%) who underwent up-front resection developed complications (p = 0.287).[7] The cohort had a greater degree of pharmacologic (bevacizumab, sunitinib,

sorafenib) and surgical (cytoreductive nephrectomy and recurrent metastectomy) heterogeneity than our analyzed cohort, and utilized agents which have in the long run been shown not to be as effective as sunitinib (sorafenib, bevacizumab) which could account for the difference.[20] In a follow up study from the same group, Chapin et al with a larger cohort (70 patients with targeted therapy prior to CN versus 103 patients with immediate CN), noted that use of presurgical targeted therapy compared to immediate surgery was associated with a greater incidence of complications > 90 days, (15.9% versus 3.8%, p = 0.002), multiple complications (p = 0.013), and wound complications (p < 0.001), though not associated with either greater risk of complications overall (65.7% versus 51.4%; p = 0.085), or high grade (Clavien ≥ 3) complications (29.4% versus 30.2%; p = 0.999). Multivariable analysis revealed that presurgical targeted therapy was a predictive factor for wound complication (OR 4.14, p = 0.003) but not for overall complications (p = 0.237).[21]

In our multivariable analysis we noted that increasing age was the only factor independent factor associated with development of surgical complications (HR 1.059, p = 0.040). Our results in this regard are similar to a recently published report by Pal et al, who analyzed 219 patients with mRCC (median age 58, and 70% with prior CN) according to age-based cohorts and examined number of lines of therapy rendered for each patient, and reason for discontinuation and noted that patients age ≥ 75 years received fewer lines of systemic therapy as compared to other age-based subsets, and more frequently discontinued therapies due to toxicity.[22] Similarly, Abdollah et al, examining the Florida inpatient database, noted that more advanced age was an independent predictor for higher risk of in-hospital mortality, complications, and transfusions (p < 0.001) in patients undergoing CN for mRCC.[19]

It should be noted that the neoadjuvant TKI group was more likely to receive partial CN, lending to an increased risk of postoperative urine leak (14.6%). This complication would not be expected in those undergoing radical CN, which comprised 96.3% of the adjuvant TKI group. TKI therapy has the potential to alter angiogenesis, revascularization and epithelialization. These factors theoretically may delay healing of the collecting system and contribute to postoperative urine leak.[23] With partial nephrectomy subjects removed from the analysis, a statistical difference remained in the prevalence of high grade (Clavien ≥ 3) 25% versus 0%, p = 0.026. Our neoadjuvant group had a similar proportion of open versus MIS approaches to our primary surgical group (p = 0.776).[8,24] Other groups that have compared outcomes of open and laparoscopic CN have noted no significant difference in complication rates between the two approaches.[25,26]

Similar rates of TKI-related toxicities were noted in patients receiving TKI therapy, regardless of surgical status. Undergoing surgery for mRCC did not appear to increase the severity or frequency of TKI toxicities. These findings suggest that in patients with good performance status where the dominant tumor volume is in the primary lesion, primary CN may be considered with the knowledge that proceeding with surgery may not increase frequency or severity of TKI-related toxicity, which is often cited as an important concern with proceeding with primary cytoreductive surgery.[27,28] We feel that it is important that the management of mRCC patients who are considered for surgery and even in the post-surgical period, is carried out in a closely coordinated and multidisciplinary fashion, where adherence to principles of treatment such as maintaining patient dose and appreciation of and early intervention for toxicity and close monitoring of delayed complications related to the downstream effects of suppression of VEGF signaling in endothelial cells (such as impaired wound healing, GI toxicity and perforation, and cardiovascular sequelae) is vigorously maintained.[11,23,27]

Our study is limited by its retrospective design and the inherent biases and limitations of the analysis. While not significant, a trend toward utilization of primary TKI therapy was noted in patients with greater number of metastatic sites which may have driven patient selection. Our analysis was also limited by the sample size which limited the power of our analysis. Therefore, comparisons among the groups are taken with caution. Nonetheless, the study is strengthened by the multicenter approach and the inclusion of all groups of patients (primary/neoadjuvant and post-surgical groups) and the analysis of toxicities. In addition, our cohort, the largest single agent group to examine impact of timing of medication on surgical complications, and timing of surgery on medication toxicity adds to the growing body of literature on the topic of primary targeted therapy and suggests that primary systemic therapy is associated with an increased rate of high grade complications, yet primary cytoreductive surgery does not impact degree or severity of toxicities. Such information should be of use in the counseling of patients prior to receiving systemic or primary cytoreductive nephrectomy. Ultimately, further insight on the interaction between systemic therapy and cytoreductive surgery should be provided by randomized clinical trials currently underway by the Assistance Publique-Hôpitaux de Paris and the European Organization Research and Treatment of Cancer.[28-30]

Conclusion

Patients receiving neoadjuvant TKI therapy prior to planned CN experienced more high grade surgical complications. Furthermore, undergoing cytoreductive nephrectomy did not increase the prevalence of TKI-related toxicities. The potential for increased high grade surgical complications after primary systemic therapy requires further investigation and may impact clinical decision making and pretreatment counseling. □

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