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Neoadjuvant SABR for Renal Cell Carcinoma Inferior Vena Cava Tumor Thrombus—Safety Lead-in Results of a Phase 2 Trial

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Abstract

Purpose: To evaluate the feasibility, safety, oncologic outcomes, and immune effect of neoadjuvant stereotactic radiation (Neo-SAbR) followed by radical nephrectomy and thrombectomy (RN-IVCT).

Methods and Materials: These are results from the safety lead-in portion of a single-arm phase 1 and 2 trial. Patients with kidney cancer (renal cell carcinoma [RCC]) and inferior vena cava (IVC) tumor thrombus (TT) underwent Neo-SAbR (40 Gy in 5 fractions) to the IVC-TT followed

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by open RN-IVCT. Absence of grade 4 to 5 adverse events (AEs) within 90 days of RN-IVCT was the primary endpoint. Exploratory studies included pathologic and immunologic alterations attributable to SAbR.

Results: Six patients were included in the final analysis. No grade 4 to 5 AEs were observed. A total of 81 AEs were reported within 90 days of surgery: 73% (59/81) were grade 1, 23% (19/81) were grade 2, and 4% (3/81) were grade 3. After a median follow-up of 24 months, all patients are alive. One patient developed de novo metastatic disease. Of 3 patients with metastasis at diagnosis, 1 had a complete and another had a partial abscopal response without the concurrent use of systemic therapy. Neo-SABR led to decreased Ki-67 and increased PD-L1 expression in the IVC-TT. Inflammatory cytokines and autoantibody titers reflecting better host immune status were observed in patients with nonprogressive disease.

Conclusions: Neo-SAbR followed by RN-IVCT for RCC IVC-TT is feasible and safe. Favorable host immune environment correlated with abscopal response to SABR and RCC relapse-free survival, though direct causal relation to SABR has yet to be established.

Introduction

Radical nephrectomy (RN) and thrombectomy are the standard of care for renal cell carcinoma (RCC) that manifests with inferior vena cava (IVC) tumor thrombus (TT). However, surgery is associated with high perioperative complications[1] and recurrence rates.[2] Adjuvant tyrosine kinase inhibitors showed limited efficacy for advanced RCC.[3] Therefore, novel approaches to reduce recurrence rates for patients with RCC IVC-TT are needed.

Contemporary reports indicate that RCC is sensitive to SABR.[4,5] SAbR also has immunogenic effects that can induce immunogenic tumor cell death and initiate tumor antigen cross-presentation.[6-8] Therefore, we initiated a phase 1-2 trial of neoadjuvant SABR (Neo-SAbR) to IVC-TT followed by RN IVC thrombectomy (IVCT). We hypothesized that this approach would be beneficial for the following reasons: induction of RCC cell death in the IVC-TT, thus reducing recurrent metastatic disease secondary to live tumor microemboli shed during surgery; a decrease in local intra-IVC recurrence secondary to microscopic positive IVC margins or wall invasion; and induction of an immune response to RCC. We performed a preplanned analysis after the safety lead-in phase 1 of this trial, which we report herein.

Methods and Materials

Patients with locally advanced or metastatic RCC, or both, and radiographic evidence of renal tumor with a Mayo level I or higher IVC-TT[9] were enrolled according to the institutional review board—approved and registered (NCT02473536) clinical trial protocol (Appendix E1).

Baseline evaluation included complete staging with cross-sectional imaging (Fig. 1A-C). Neo-SAbR treated the IVC-TT only with 40 Gy in 5 fractions (Fig. 1D-F). After SABR, patients underwent open RN-IVCT by a high-volume surgeon who treats >3 RN-IVCT cases per year.[10] Response and progression were evaluated according to the Response

Evaluation Criteria in Solid Tumors version 1.1. Adverse events (AEs) were evaluated using Common Terminology Criteria for Adverse Events version 4.0. Each AE was graded, evaluated, and deemed unrelated, possibly related, probably related, or definitely related to SAbR and surgery by the principal investigators and reviewed by both the departmental and institutional data safety and monitoring committee.

The lead-in phase's primary endpoint was safety—absence of grade 4–5 AEs within 90 days of RN-IVCT. Exploratory analysis included pathologic and immunologic alterations in the primary tumor, irradiated thrombus, and patient sera, some of which were not prespecified in the clinical trial protocol. Detailed methods for pathology and immune assays are available in Appendix E2.

Results

Seven patients with newly diagnosed RCC with Mayo level I-II IVC-TT were enrolled in the trial (Table 1). One patient was withdrawn from the trial because of liver metastasis discovered during surgery, which was aborted. No other neoadjuvant treatments were administered to the patients until progression. All patients completed SAbR treatment as planned and underwent surgery within 4 to 14 days of SAbR. Median surgery duration was 190 minutes (range, 153-243 minutes). No cardiopulmonary bypasses or thoracotomies were performed. Median estimated blood loss was 400 mL (range, 100-1200 mL); 3 patients required blood transfusion. Median postoperative hospital length of stay was 4 days (range, 3-10 days). No intraoperative complications were noted. No increased intraoperative technical difficulties were attributed to Neo-SABR, nor were there increases in edema or fibrosis notable during surgery as a result of recent SABR.

Adverse events

Eighty-one total AEs were reported within 90 days of surgery (Table 2): 73% (59/81) were grade 1, 23% (19/81) were grade 2, and 4% (3/81) were grade 3. The most common SAbR-associated AE was nausea, the highest being grade 2. The most common AEs after surgery were abdominal pain and constipation. Eighteen percent (15/81) and 33% (27/81) of AEs were deemed to be associated with SABR and surgery, respectively. The most clinically substantial AEs observed were upper respiratory tract infection and upper extremity deep vein thrombosis. One patient was readmitted within 90 days of surgery because of acute cholecystitis and underwent a cholecystectomy. Individual AEs are listed in Table E1.

Oncologic outcomes

After a median follow-up of 24 months (range, 12-37 months), all patients were alive. One of 3 nonmetastatic patients developed lung metastasis 12 months after surgery, and another patient who progressed immediately after surgery eventually exhibited complete response with subsequent IL-2 treatment. An abscopal response was observed in 1 patient who had a presumed 2-cm growing lung metastasis with multiple small nodules, which regressed 6 months after surgery (Fig. 2); the patient remains free of disease at 3-year follow-up without any additional therapy. Partial response in multiple lung nodules was measured in another patient; however, disease eventually progressed to other sites (Table E2).

Pathology and immune response correlates

The immunohistochemistry characteristics of nonirradiated primary tumor are compared with irradiated IVC-TT in Table 3. Of the 5 patients with clear cell RCC pathology, 4 showed decreased or unchanged Ki-67 expression, whereas 1 patient showed an increase. PD-L1 expression on the tumor cell membrane was increased in 3 patients and unchanged in 3 patients (Figure E1, Table 3). No increase in tumor PD-L1 was observed in nonradiated primary and TT control samples (n = 6; Table E3).

Most of the cytokines investigated were upregulated at baseline, especially in patients who progressed (Fig. E2). Despite clear heterogeneity in IgG autoreactivity for each patient at baseline, IgG autoantibody signals tended to increase from baseline, primarily in patients who did not progress (Fig. 3A). The difference in the percent of autoantibodies increased significantly at follow-up visits 3 and 4 (Kruskal-Wallis test, $P = .0495$; Fig. 3B). Enzyme-linked immunosorbent assay showed that serum titers of autoantibodies against carbonic anhydrase IX increased significantly ($P = .013$-$.019$) during follow-up only in patients who did not progress (Fig. 3C).

Discussion

To our knowledge, this is the first report from a prospective trial evaluating SAbR for RCC IVC-TT. We observed minimal AEs associated with SABR, the most common of which was nausea. No intraoperative complications or technical difficulties performing surgery on a recently irradiated field were reported. Three patients had severe (grade 3) AEs, which is consistent with reported complication rates of 15% to 35% after RN-IVCT.[1,11,12] Ultimately, no grade 4 to 5 AEs were reported, thus meeting the lead-in phase primary endpoint. The long-term toxicity of Neo-SABR and surgery in this setting remains to be determined.

Our cohort small size makes discussing oncologic outcomes premature. Nevertheless, within 12 months, only 1 patient developed new metastatic disease. Furthermore, we observed a clear abscopal effect with complete regression of a suspected pulmonary metastases (Fig. 2) in 1 of the 3 metastatic patients, with another showing a partial response. Wersäll et al[13] reported an abscopal effect in 4 of 28 patients (14%) treated with SAbR for RCC. The apparently higher rates of abscopal responses in 2 of the 3 patients with metastatic disease in our cohort, without any immune-adjuvants, might be attributable to using SAbR on the tumor thrombus, which is accessible to dendritic cells in the blood flowing through the thrombus continuously.

The lower Ki-67 levels seen in tumor cells in irradiated IVC-TT supports the clinical rationale that Neo-SAbR renders tumor emboli incapable of forming metastases. Interestingly, there was no change in CD4, CD8, or other tumor-infiltrating immune cells, likely because of the dynamics of continuously flowing blood through the irradiated TT. Patel et al.[14] suggested that irradiation can affect PD-L1 expression in sarcomas; we observed a conversion from negative to positive (> 1%) tumor PD-L1 expression in 1 patient with negative baseline PD-L1 and a higher percentage of cells expressing PD-L1 in the irradiated thrombus than in their nonirradiated primary tumor counterpart.[15] In contrast,

we observed no difference in tumor PD-L1 staining between primary tumors and their corresponding nonirradiated thrombus in a control population.

Despite a substantial heterogeneity in both proin-flammatory and anti-inflammatory cytokine profiles in our patients at baseline, we noticed a trend toward higher plasma cytokine levels in patients whose disease eventually progressed, suggesting that the host's baseline immune state may influence response or lack thereof to radiation. Higher levels of cytokines are correlated to a dysfunctional immunity, perhaps mediated by higher levels of myeloid-derived suppressor cells. Moreover, it is also recognized that a sera cytokine increment has been associated with poor prognosis to cancer therapy.[16]

The observed increased trend toward nonspecific (Fig. 3A-B) and specific IgG autoantibodies (Fig. 3C) in patients who did not progress is consistent with previous reports, which suggests that the increase in the production of autoantibodies reflects greater immunologic reactivity in patients with cancer, and it might predict durable response.[17] Immune-related AEs are correlated with objective response to immunotherapy, perhaps because many tumor antigens are also autoantigens.[18,19] This response could be enhanced further by eliminating the immunosuppressive effect of cancer by radiation and surgery. Although a causal relation to SABR cannot be established because of the lack of a control arm, this observation is hypothesis generating and calls for further validation.

Our study has several limitations. First, this is a small heterogeneous group of patients. Second, all surgeries were performed by 1 high-volume surgeon, which could affect both complication rates and survival.[10] Third, the primary tumors were unavoidably exposed to low doses of radiation owing to proximity to the target. Finally, we obtained only 1 sample from each primary tumor; therefore, tumor heterogeneity might have affected our results.

Conclusions

Overall, the results of this phase 1 trial indicate that Neo-SAbR for RCC IVC-TT is feasible and safe and, therefore, should be evaluated for efficacy in a phase II setting, which is ongoing (NCT02473536).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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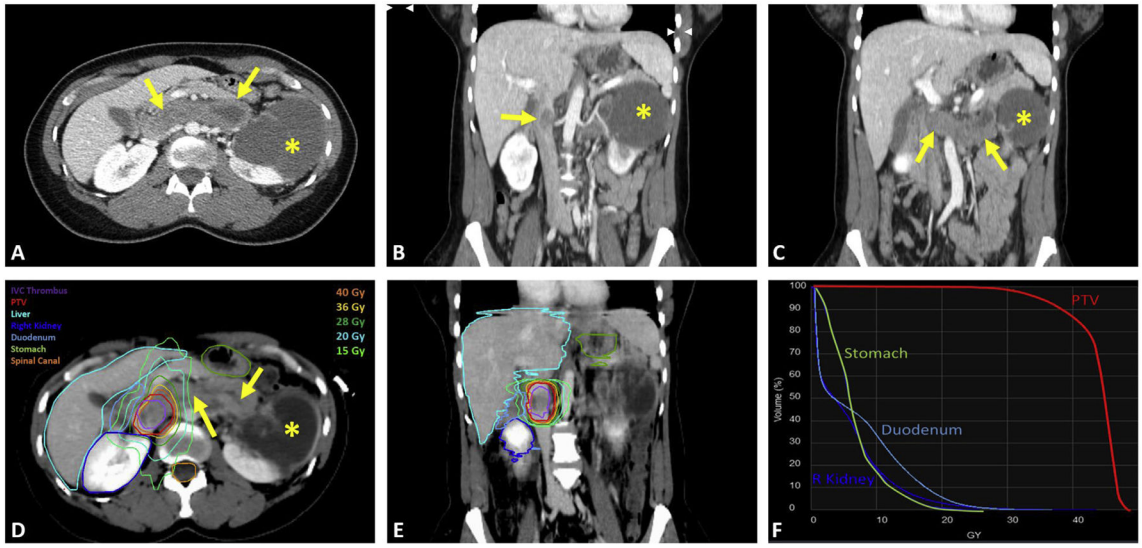


Fig. 1.

A representative image of IVC-TT (patient 2) with left kidney cancer receiving SAbR to the IVC-TT. (A) Axial image and (B, C) coronal reconstructions of a contrast-enhanced computed tomography examination showing the left kidney mass (yellow asterisk) and a tumor thrombus (yellow arrows) extending from the left kidney hilum to the inferior vena cava. (D, E) Axial and coronal views of the SAbR treatment plan (40 Gy in 5 fractions) showing PTV and normal structures with isodose lines. Dose levels are shown in the right panel in (D). (F) Dose-volume histogram showing dose-volume relationships for PTV, stomach, duodenum, liver, and right kidney. *Abbreviations:* PTV = planning target volume; TT = tumor thrombus.

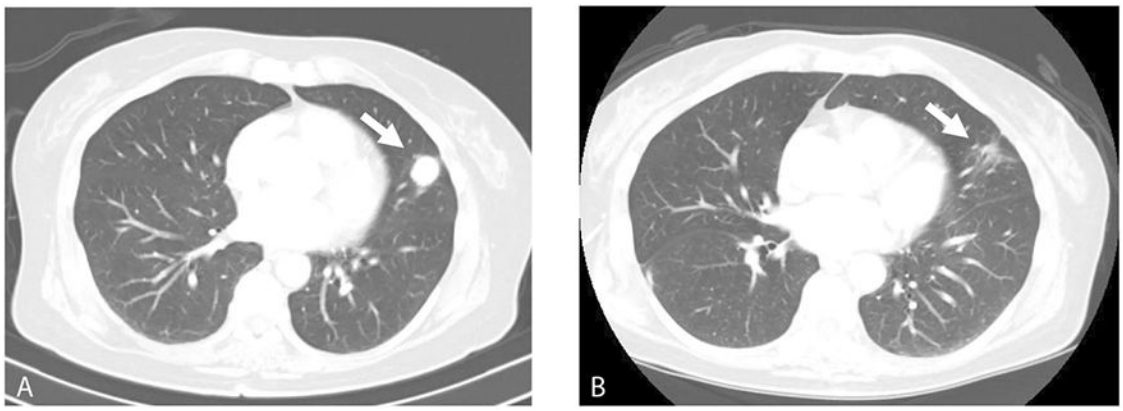
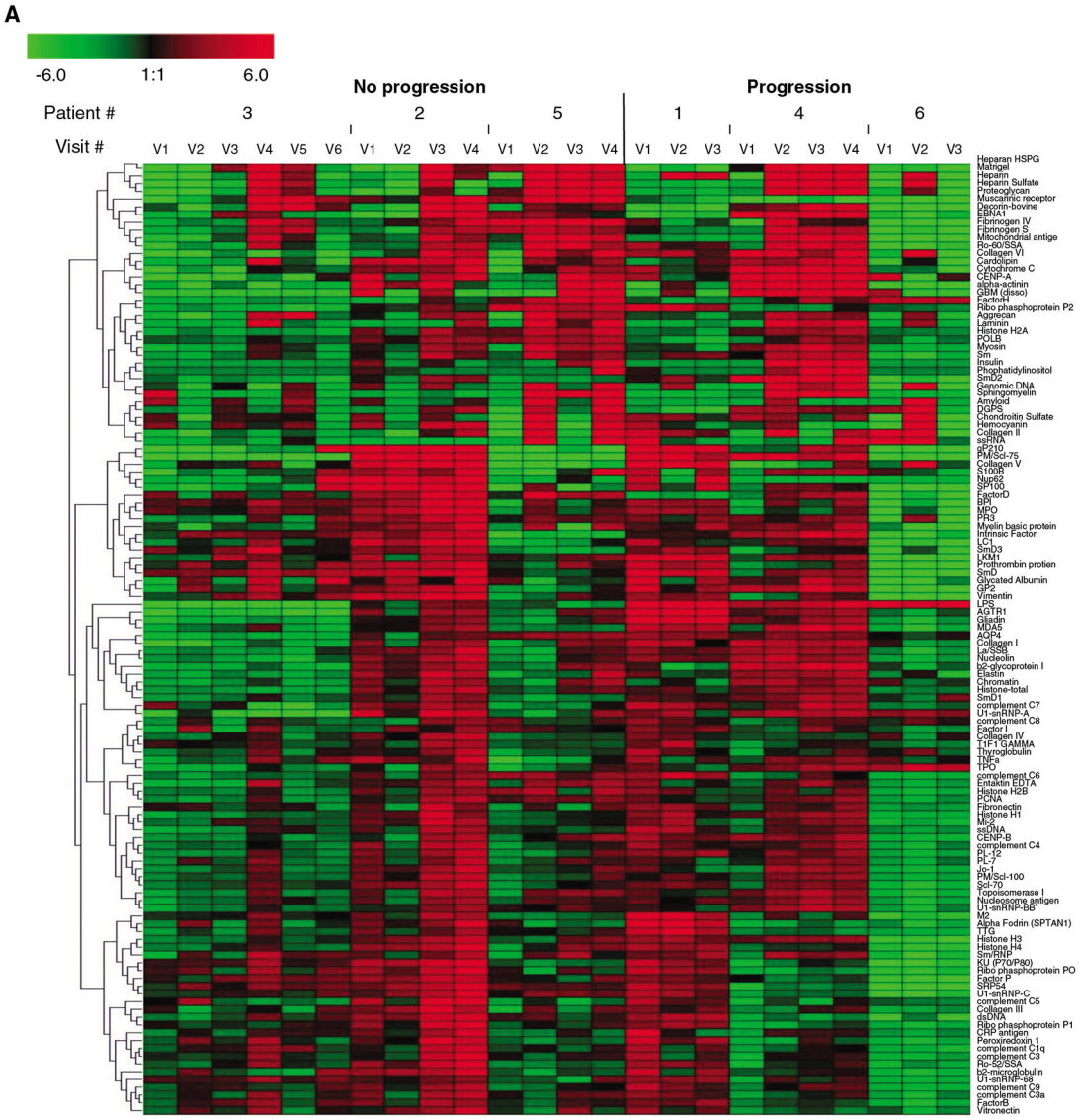


Fig. 2.

Computed tomography (CT) of a suspected left pulmonary metastasis from renal cell carcinoma. (A) Axial CT imaging obtained 10 weeks before surgery and before initiating SABR of the IVC-TT shows a 2-cm noncalcified nodule (arrow) in the lingular segment of the left upper lobe. (B) Follow-up imaging of the left upper lobe nodule obtained 7 months after surgery demonstrates complete resolution of the lung nodule (arrows) with minimal residual parenchymal scarring. *Abbreviations:* IVC = inferior vena cava; TT = tumor thrombus.



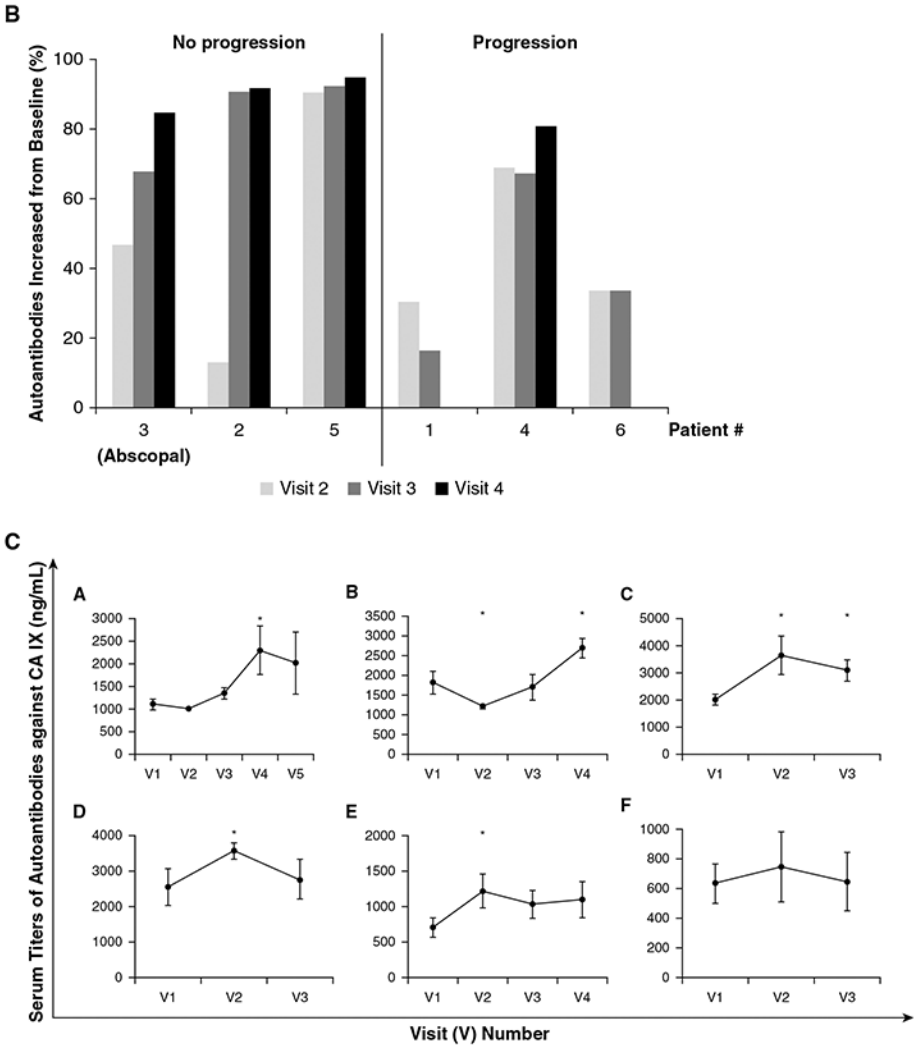


Fig. 3.

Autoantigen arrays. (A) Heatmap of an array of 128 autoantigens demonstrates that IgG autoantibody production is increased during the follow-up period, mainly in patients who did not progress. (B) Percent changes in the intensity of autoantibody signals are significant only in patients who did not progress after treatment, but not in patients with progressive disease (Kruskal-Wallis test, $P = .049$). (C) Serum titers of autoantibodies against CA IX increased over time ($P = .013$-$.019$, Kruskal-Wallis test) in patients who did not progress (A-C) than in patients with progressive disease (D-F). (A) Patient 3. (B) Patient 2. (C) Patient 5. (D) Patient 1. (E) Patient 4. (F) Patient 6. Values are reported as mean ± standard deviation (SD) calculated from 3 to 4 independent experiments. *Abbreviations:* CA = carbonic anhydrase; V = visit; V1 = baseline; V2 = postoperative; V3 = first follow-up; V4 = second follow-up; V5 = third follow-up. *The difference between each corresponding time point and the baseline (V1) is statistically significant ($P < 0.05$).

Table 1

Cohort and tumor characteristics

	Patient number					
	1	**2**	**3**	**4**	**5**	**6**
Sex	Female	Female	Female	Male	Male	Male
Age (y)	41	39	60	49	69	52
ECOG performance status	0	0	1	1	1	1
ASA score	2	3	4	3	3	4
Thrombus level (Mayo classification[10])	II	I	II	II	II	I
Largest tumor diameter (cm)	10	6.9	12	14.6	10.8	7.3
cT	3b	3b	4	3b	3b	3b
cN	1	0	1	0	0	0
cM	1	0	1	0	0	1
Clinical stage	IV	III	IV	III	III	IV
IMDC risk group (if applicable)	Intermediate	NA	Poor	NA	NA	Intermediate

Abbreviations: ASA = American Society of Anesthesiologists; ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Consortium; NA = not applicable.

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Table 2

Adverse events

Features		Preoperative	Postoperative	Total
Total number		10% (8/81) *	90% (73/81) †	100% (81/81)
Grade				
1		75% (6/8) *	73% (53/73) †	73% (59/81)
2		25% (2/8) *	23% (17/73) †	23% (19/81)
3		0% (0/8) *	4% (3/73) †	4% (3/81)
≥4		0% (0/8) *	0% (0/73) †	0% (0/81)
Attribution		**SABR**	**Surgery**	**Total**
Treatment related ‡				
Yes	Any	18% (15/81)	33% (27/81)	43% (35/81)
	<Grade 3	100% (15/15)	93% (25/27)	98% (79/81)
	Grade 3	0% (0/15)	7% (2/27)	2% (2/81)
No	Any	82% (66/81)	67% (54/81)	57% (46/81)

Abbreviation: AE = adverse event.

* AEs observed after initiation of SABR and before surgery date.

† AEs observed after surgery.

‡ AEs may be attributed to both surgery and SABR.

Table 3

acteristics of the nonirradiated primary tumor versus corresponding irradiated tumor thrombus samples *

Ki-67		PD-L1 tumor membrane		PD-L1 in inflammatory cells		PD-1 in inflammatory cells		CD20		CD4		CD8		CD68		CD31	
Primary	Thrombus	Primary	Thrombus	Primary	Thrombus	Primary	Thrombus	Primary	Thrombus	Primary	Thrombus	Primary	Thrombus	Primary	Thrombus	Primary	Thrombus
2%	↑	0	↑	0	↑	1	~	Rare	~	Mod	↑	Low	~	Mod	↑	High	↓
2%	~	1	~	3	~	0	~	Rare	~	Mod	~	Low	~	Mod	~	Low	~
5%	~	1	~	1	~	1	~	Rare	~	Mod	~	Low	~	High	~	Low	↑
15%	↓	3	↑	3	~	3	~	Mod	↓	High	↓	Mod	~	High	↓	Low	~
15%	↓	3	↑	3	~	3	~	Low	~	High	↓	High	↓	High	↓	Mod	~
20%	~	3	~	3	~	3	~	Low	~	High	~	Mod	~	High	~	Mod	~

al cell carcinoma; ISUP = International Society of Urologic Pathologists; MTSCC = mucinous tubular and spindle cell carcinoma; ~ = no change; ↓ = decrease; ↑ =

vas assessed using a 4-tier criteria system, as follows: 0 (less than 1%), 1 (1%-5%), 2 (5%-10%), and 3 (higher than 10%). The expression of cellular markers for also evaluated using a 4-tier criteria system, as follows: rare (<5%), low (5%-20%), moderate (20%-50%), and high (>50%).