



# Inferior vena cava thrombectomy for renal cell carcinoma: perioperative systemic therapy, cytoreductive nephrectomy, and complex cases

Shagnik Ray, Eric A. Singer, Shawn Dason

Division of Urologic Oncology, The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

Correspondence to: Shawn Dason, MD. 915 Olentangy River Road, Suite 3100, Columbus, OH 43212, USA. Email: Shawn.dason@osumc.edu.

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## Introduction

We read the accompanying article by Dr. Ciancio and colleagues and commend their contributions to the operative management of renal cell carcinoma (RCC) with venous tumor thrombus (1). In this editorial, we aim to highlight some additional areas of interest that complement their comprehensive review. This includes:

- (I) Perioperative systemic therapy for patients undergoing inferior vena cava (IVC) thrombectomy who do not have metastatic disease;
- (II) Combined cytoreductive nephrectomy (CN) and IVC thrombectomy;
- (III) Robotic IVC thrombectomy;
- (IV) Decision-making in complex tumor thrombectomy cases.

## Perioperative systemic therapy

Modern systemic therapy with immune checkpoint inhibitors and tyrosine kinase inhibitors has significantly improved survival for metastatic RCC (mRCC). Unsurprisingly, multiple studies are underway to assess these medications in the adjuvant setting for non-metastatic patients at high-risk of recurrence, such as those with IVC tumor thrombus. *Table 1* details some key attributes of active adjuvant immuno-oncology (IO) trials.

Conflicting and immature efficacy data emphasizes the need for further prospective investigation to assess which patients may benefit from adjuvant therapy. KEYNOTE-564 included patients with clear cell RCC that was locoregional or metastatic and amenable to complete resection [tumor stage 2 with nuclear grade 4 or sarcomatoid, tumor stage 3 or higher, regional lymph-node involvement, or stage M1 with no evidence of disease (NED)] (2,3). Nine hundred and ninety-four patients were randomized to receive 1 year of adjuvant pembrolizumab *vs.* placebo. Although overall survival (OS) results are still immature, recurrence-free survival (RFS) was significantly improved compared with placebo [hazard ratio (HR) =0.63; 95% CI: 0.50–0.80].

While KEYNOTE-564 does provide an adjuvant option following nephrectomy and IVC thrombectomy, the results of multiple parallel adjuvant IO trials were negative. Immotion010 included 778 patients with RCC with a clear cell or sarcomatoid component and increased risk of recurrence (T2 Fuhrman grade 4, T3a grade 3–4, T3b–c any grade, T4 any grade, TxN+ any grade; M1 no evidence of disease category including patients with synchronous metastatic disease to the adrenal gland or lung, or metachronous metastatic disease to the lung, lymph node, or soft tissue, with recurrence occurring more than 12 months following initial nephrectomy). Patients were randomized to adjuvant atezolizumab (once every 3 weeks

**Table 1** Select ongoing trials assessing the role of adjuvant immune-oncology therapy for locally advanced RCC

Trial name (clinical trial number)	Intervention (primary endpoint)	Sample size (recruitment status)	Outcome	% M1 NED	% Clear cell
Keynote 564 (NCT03142334)	Adjuvant pembrolizumab vs. placebo (DFS)	994 (complete)	Significantly improved DFS with HR 0.63, 95% CI: 0.50–0.80 at 30 months	5.8%	100%
IMmotion10 (NCT03024996)	Adjuvant atezolizumab vs. placebo (DFS)	778 (complete)	No statistically significant DFS benefit at 45 months	14.4%	93.3%
PROSPER RCC (NCT03055013)	Neoadjuvant and adjuvant nivolumab vs. observation (DFS)	766 (complete)	No statistically significant DFS benefit at 16 months	3%	78%
Checkmate 914 (NCT03138512)	A: Nivolumab and ipilimumab vs. placebo B: Nivolumab and ipilimumab vs. nivolumab and placebo vs. placebo (DFS)	1,641 (complete)	No statistically significant DFS benefit at 37 months	–	100%
RAMPART (NCT03288532)	Durvalumab and tremelimumab vs. Durvalumab vs. observation (DFS/OS)	1,750 (currently recruiting)	–	–	–

RCC, renal cell carcinoma; NED, no evidence of disease; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

for 16 cycles) or placebo after undergoing nephrectomy or nephrectomy with metastasectomy (M1 resected with no evidence of disease). Disease-free survival (DFS) did not differ between groups (4).

The CheckMate 914 trial assessing adjuvant nivolumab with ipilimumab versus placebo in patients with predominant clear cell histology, pathological tumor-node-metastasis (TNM) stage T2a [grade (G) 3 or 4] N0M0, T2b (any G) N0M0, T3 (any G) N0M0, T4 (any G) N0M0, or any T (any G) N1M0; and no clinical/radiological evidence of residual disease or distant metastases additionally did not meet the primary endpoint of DFS over a median follow up of 37.0 months (5).

While not strictly an adjuvant study, the PROSPER RCC trial enrolled patients with clinical stage  $\geq$  T2 or TanyN+ RCC (of both clear cell and non-clear cell histologies) planned for nephrectomy (partial or radical) as well as select oligometastatic disease if the patient could be rendered ‘no evidence of disease’ within 12 weeks of surgery who were randomized to 1 dose of neoadjuvant and 9 doses of adjuvant nivolumab, with RFS similar between arms (HR =0.97; 95% CI: 0.74–1.28; P1-sided =0.43) and the trial closed secondary to futility (6).

Although less commonly studied, neoadjuvant therapy would be of great utility if it facilitated subsequent IVC thrombectomy. A multicenter retrospective review recently reported on 19 patients who underwent neoadjuvant sunitinib prior to IVC thrombectomy. They found a

median decrease in tumor thrombus size of 1.3 cm (7). The tumor level itself decreased in 8/19 (42.1%) patients and remained stable in 10/19 (52.6%). Limited differences in perioperative outcomes or approach were found with preoperative systemic therapy. The NAXIVA phase II prospective trial assessing 20 patients with clear cell RCC with tumor thrombus undergoing up to 8 weeks of neoadjuvant axitinib found that 7/20 patients (35%) had a reduction in thrombus level (6/16 with IVC tumor thrombus and 1/4) with renal vein without vena cava tumor thrombus), with 15/20 patients having some reduction in the length of the thrombus, and notably with 7/17 patients undergoing surgery that was “less invasive” than initially planned (8).

Limited data exists for neoadjuvant systemic therapy with contemporary systemic therapy regimens. Case reports exist of neoadjuvant nivolumab/ipilimumab resulting in a complete response of IVC thrombus (9). While the Checkmate 214 trial assessing nivolumab/ipilimumab in advanced RCC was not a neoadjuvant study, in those with a primary tumor *in situ*  $\geq$ 30% primary tumor reduction was achieved in 35% of patients receiving ipilimumab/nivolumab vs. 20% with sunitinib control in this study. This indicates that doublet neoadjuvant therapy would be preferred if it is to be used (10). Neoadjuvant lenvatinib and pembrolizumab prior to IVC thrombectomy is currently being studied in an actively recruiting clinical trial (NCT05319015). A trial assessing neoadjuvant stereotactic

ablative radiotherapy (SABR) prior to IVC thrombectomy trial is also recruiting (11,12).

### CN with IVC thrombectomy

CN involves surgical resection of the primary tumor in the setting of known mRCC. Observational data generally indicates that CN is commonly performed and that it is associated with improved survival in mRCC (13-15). In the specific context of CN in patients with inferior vena cava tumor thrombus (IVCTT), there exists retrospective data supporting this practice. A retrospective review of 76 patients [where 30 (40%), 31 (41%), and 15 (20%) of patients had a level II, III, and IV IVCTT respectively] found a perioperative mortality of 6.6% with an overall and major postoperative complication rate of 37% and 7.8% respectively (16). Ninety percent of the 60 patients available for review underwent post-operative systemic therapy, with a median survival time of 14 months. Miyake *et al.* retrospectively reviewed 75 patients [where 11 (15%), 33 (44%), 24 (32%) and 7 (9%) had a level II, III, and IV IVCTT respectively] who subsequently underwent systemic therapy with cytokine therapy alone [25 patients (33%)], molecular targeted therapy alone [27 patients (36%)], or both [23 patients (31%)] (17). Median OS was 16.2 months, without differences noted based on IVCTT level, with significantly improved survival for those undergoing molecular targeted therapy or molecular targeted therapy in conjunction with cytokine therapy compared with cytokine therapy alone. Taken together keeping in mind their retrospective limitations, these studies suggest that CN for IVCTT is feasible with an acceptable perioperative risk profile.

Decision-making surrounding when to perform CN in the patient with IVCTT is complex. Although systemic therapy is effective in IVC thrombi (9), complete response is exceedingly unlikely (10). Primary radiation treatment has also shown promise in IVC thrombi (11) but clear indications await ongoing prospective studies (18). Three recent prospective studies inform our practice of CN in patients with IVCTT: CARMENA (19,20), SURTIME (21), and NAXIVA (8). CARMENA (19,20) randomized 450 patients to receive CN followed by sunitinib or CN alone. It was noted that patients with 1 International Metastatic RCC Database Consortium (IMDC) risk factor had a slight benefit in OS in the CN group (30.5 *vs.* 25.2 months, nonsignificant) while those with 2 or more IMDC risk factors had a shorter survival in the CN group (16.6 *vs.*

31.2 months,  $P=0.015$ ). SURTIME (21) randomized 99 patients to upfront CN followed by sunitinib *vs.* upfront sunitinib followed by CN in those without progressive disease. Those with upfront CN in SURTIME had a shorter median OS (15.0 *vs.* 32.4 months) and a lower rate of actually receiving sunitinib (80% *vs.* 98%). Finally, NAXIVA (8) enrolled 20 patients with resectable RCC and an IVC thrombus who were treated with up to 8 weeks of neoadjuvant axitinib. In the study period, no patients had progression or suffered significant sequelae of their IVC thrombus. Although these studies have their respective limitations, they lend support to the paradigm that: (I) patient selection for CN is paramount, (II) treatment with systemic therapy upfront and consideration of deferred surgery may be appropriate for those not best suited to upfront CN and IVC thrombectomy, and (III) limited sequelae will develop from a period of preoperative systemic treatment in the patient with an IVC thrombus.

Contemporary indications for CN include:

- (I) Limited metastatic disease that would be amenable to active surveillance following CN;
- (II) Limited metastatic disease that can be controlled completely with metastasis directed therapy (MDT) following CN;
- (III) 1 IMDC risk factor with the majority of tumor burden located in the kidney (22);
- (IV) Oligoprogressive disease within the kidney following upfront systemic therapy;
- (V) Significant local symptoms, particularly those that require hospitalization and prevent receipt of systemic therapy.

Relative indications that may factor into decision-making specifically in the patient with an IVC thrombus include:

- (I) Therapeutic anticoagulation is required but cannot be administered due to significant hematuria;
- (II) Proximity to hepatic veins or diaphragm where progression may significantly increase surgical complexity;
- (III) Friable thrombus at high risk of embolization;
- (IV) Obstructive venous sequelae relating to IVC thrombus.

Advances in systemic therapy have made upfront systemic therapy a more feasible alternative to upfront CN and IVC thrombectomy. Upfront systemic therapy should be considered in every patient being considered for upfront CN. Patients treated with upfront systemic therapy can often be considered for deferred CN in the event of appropriate response. Relative indications for upfront

systemic therapy rather than upfront CN include:

- (I) Predominantly extrarenal disease burden;
- (II) High surgical morbidity;
- (III) Poor performance status and/or poor IMDC risk.

### **Practical incorporation of robotic surgery for IVC thrombectomy**

Selected IVC thrombectomy cases are now being regularly performed with robotic assistance. Robotic renal surgery has a number of potential benefits over the open approach including reduced blood loss, less pain, and faster convalescence (23). Robotic assistance is most relevant to level 0–II IVC thrombus cases where mortality is low and these perioperative benefits are most relevant. Although level III–IV robotic IVC thrombectomy has been described (24), the clinical benefit of robotic assistance in level III–IV cases remains undefined given that robotic assistance would not be expected to impact major complications or mortality rate (25).

Although the principles of robotic IVC thrombectomy mirror the open approach, a number of specific considerations apply. The surgeon considering robotic IVC thrombectomy needs to consider case selection, overcoming robotic limitations during intraoperative challenges, difficulty with left-sided tumors, preparing for open conversion, how to involve any necessary consulting surgeons that cannot perform robotic surgery, hemodynamic difficulties of pneumoperitoneum and a fixed position, inability to leave an open abdomen, and access difficulties for transesophageal echocardiography and emergent cardiopulmonary bypass (CPB).

Initial case selection for robotic IVC thrombectomy is important and the ideal patient is one with a right-sided level 0–II tumor thrombus, a normal height and weight, absence of a bulky primary tumor, limited adenopathy, a thrombus that is not especially friable and does not significantly contact the IVC wall circumferentially, no anticipated vascular reconstruction, and has a cephalad extent that will not require significant short hepatic division or liver mobilization. Surgical technique for robotic IVC thrombectomy is beyond the scope of this editorial but has been described in detail elsewhere (26).

### **Decision-making surrounding complex tumor thrombi**

Decision-making surrounding tumor thrombi can be

nuanced. In this section we discuss selected decision-making considerations. A more thorough discussion of our operative technique has been described elsewhere (26).

#### *Thrombus height and extent*

In high-level IVC thrombectomy cases, it is essential to be prepared for a difference in thrombus level and extent from what has been indicated on preoperative imaging. Thrombus height is only conclusively demonstrated at the time of transesophageal echocardiography and/or intraoperative ultrasonography. It is useful to be prepared for at least 1 level higher tumor thrombus than expected. Intraoperative findings during thrombectomy are also highly variable and need to be anticipated. The presence of a “thrombus team” consisting of cardiac anesthesia, a perfusion team, and high-volume surgeons at high volume institutions can help ameliorate such discrepancies in thrombus level.

#### *Abdominal approach for level III–IV thrombi*

An abdominal approach is often feasible for a thrombus around the hepatic veins but it can be difficult to distinguish preoperatively exactly where the diaphragm lies and whether control cephalad to a level III thrombus will be achievable safely via the abdomen. Although an abdominal approach to the supradiaphragmatic vena cava is feasible (27), there are drawbacks to this and those with a friable thrombus tip may risk intraoperative embolization. The option to perform sternotomy, CPB, and deep hypothermic arrest (DHA) should all be available for anticipated abdominal IVC thrombectomy cases when the thrombus is close to the diaphragm or at high risk of embolization.

#### *Level IV thrombi*

Thoracic dissection is generally indicated when a supradiaphragmatic IVC thrombus is present. This is conventionally accomplished with a median sternotomy as this will be very familiar to most cardiothoracic surgeons for setup of CPB and DHA.

Supradiaphragmatic thrombi may be atrial or infra-atrial. Atrial thrombi often indicate CPB/DHA with an atriotomy for extraction unless the thrombus can be milked caudally or renal artery ligation lowers the height of the thrombus.

If a level IV thrombus is infra-atrial, cephalad control for tumor thrombectomy just below the atrium may allow

for avoidance of CPB/DHA and associated sequelae. Infra-atrial IVC clamping without CPB has significant hemodynamic implications but can often be tolerated for short durations. If CPB/DHA are not used, significant back-bleeding from the hepatic veins will occur when the cava is opened. This necessitates that the thrombus be efficiently removed so that an infra-hepatic clamp can be placed and hepatic drainage restored. This approach is generally best suited to the thrombus that is suspected to be free floating. It is ideal to have CPB/DHA available for the infra-atrial level IV thrombus suspected to be adherent so that the cava can be most thoroughly inspected in a bloodless field to ensure complete clearance. Portions of the IVC can be resected for gross invasion below the major hepatic veins but debridement alone is often all that can be performed for adherence at the major hepatic vein level or higher.

## Conclusions

Advanced RCC with IVCTT is a complex disease process as succinctly detailed by Dr. Ciancio's team. Our group adds some additional considerations to be taken into account. Adjuvant and neoadjuvant therapy has been shown in both retrospective and prospective trials to have some benefit on shrinking IVCTT in both size and level, without any known survival benefit as of yet, with active prospective trials ongoing. CN in patients with IVCTT is feasible and has possible benefit in the appropriately selected patient. A robotic approach to IVC thrombectomy is possible with careful preoperative consideration of possible pitfalls to the robotic approach. The decision-making regarding IVC thrombus management in complex cases remains an area of ongoing discourse, with numerous considerations to be accounted for by the urologic oncologist.

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