



Up, Up, and Above—Tumor Thrombus in RCC

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Abstract

Intravascular tumor thrombosis is most commonly encountered in renal cell carcinoma (RCC), which alters the staging and prognosis of malignancies, indicating an advanced stage of malignancy, which can be surgically challenging during treatment course. Imaging plays a vital role in the detection of tumor thrombus and in differentiating it from bland thrombus. The Mayo Clinic thrombus classification is widely used to describe levels of inferior vena cava tumor thrombus (IVC-TT) in patients with locally advanced RCC. In this article, we review the classification, guidelines, and recent diagnostic tools for RCC with IVC tumor thrombi, and mention about the various surgical approaches for each stage of tumor thrombi.

Keywords

- ▶ IVC tumor thrombus
- ▶ RCC
- ▶ tumor thrombus

Introduction

Intravascular tumor thrombosis is defined as the extension of tumor into a vessel. It alters the staging and prognosis of malignancies, indicating an advanced stage of malignancy, which can be surgically challenging during treatment course. Tumor thrombosis occurs in various malignancies, most frequently in renal cell carcinoma (RCC), Wilms tumor, adrenal cortical carcinoma, and hepatocellular carcinoma.¹ RCC is the most common malignancy to cause tumor thrombosis of inferior vena cava (IVC). In up to 10% of all RCC cases, a thrombus is found in the renal vein or IVC.^{2,3}

The incidence of tumor extension to IVC in RCC is increasing recently, mostly due to increased detection secondary to the advances in diagnostic modalities. Imaging plays a vital role in the detection of tumor thrombus (TT) and in differentiating it from bland thrombus. The Mayo Clinic thrombus classification is widely used to describe levels of IVC tumor thrombus (IVC-TT) in patients with locally advanced RCC.⁴

In this article, we review the classification, guidelines, and recent diagnostic tools for RCC with IVC tumor thrombi, and

mention about the various surgical approaches for each stage of tumor thrombi.

Renal Cell Carcinoma

Most renal lesions are incidental, of which RCC accounts for 90% of adult renal malignancies and 2% of all cancers diagnosed worldwide.⁵ RCC is approximately twofold more common in males than females; and occurs predominantly in sixth to eighth decade of life, with median age at diagnosis around 64 years.⁶

Established risk factors include smoking, hypertension, obesity, occupational exposure like cadmium, asbestos, and syndromic associations like Von Hippel-Lindau (VHL) disease, BRCA1-associated protein-1 (BAP 1) mutant disease, Succinate dehydrogenase (SDH)- associated renal cancer, hereditary leiomyomatosis and RCC, hereditary papillary kidney cancer, Birt-Hogg-Dubé syndrome, tuberous sclerosis complex, and Cowden syndrome.⁷

Several distinct subtypes of RCC have been identified that include:^{8,9}

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- Clear cell (75–85 % tumors)
- Papillary (chromophilic; 10–15 %)
- Chromophobe (5–10 %)
- Oncocytic (3–7 %)
- Collecting duct (Bellini duct; very rare)
- Translocation RCC (rare)
- Unclassified—up to 5 %

The classic triad of RCC includes flank pain, hematuria, palpable abdominal mass. Abdominal or flank mass is associated with lower pole tumors. RCC with extension into renal veins causes scrotal varicoceles, majority being left sided, as seen in around 11% of men with RCC.¹⁰ These varicoceles typically fail to empty when the patient is recumbent. IVC involvement by tumor can produce various clinical manifestations, including lower extremity edema, ascites, hepatic dysfunction (possibly related to Budd-Chiari syndrome), and pulmonary emboli. Hematuria is observed with tumor invasion of the collecting system.

Among patients with disseminated disease, signs or symptoms may be due to metastatic tumor; most common sites include lungs, lymph nodes, bone, liver, brain, where the diagnosis is made either by biopsy of an accessible metastasis or by finding renal mass on abdominal computed tomography (CT). In some, paraneoplastic syndromes can occur due to ectopic production of hormones (e.g., erythropoietin, parathyroid hormone-related protein, gonadotropins, human chorionic somatomammotropin, adrenocorticotropic hormone-like substance, renin, glucagon, insulin).¹¹ RCC-associated hepatic dysfunction in the absence of liver metastases is an uncommon occurrence, called Stauffer syndrome,¹² occurring in up to 20% patients.

Imaging Features

Patients with suspicion of RCC should undergo imaging to diagnose and delineate the extent. Imaging of suspected cases includes ultrasonography (USG), CT, and magnetic resonance imaging (MRI).

USG

US has long been one of the primary methods for diagnostic imaging of renal lesions as it is easily repeatable, does not entail radiation, and is cost-effective. Detection rates increase with increase in lesion diameter.¹³ Also, US is useful to determine the cystic nature of a nature when CT contrast is contraindicated. Lesions appearing cystic on CT yet solid on US can in some cases turn out to be RCC, indicating complementary use of both to better characterize the underlying pathology. Resistive index on spectral Doppler measured in RCCs is significantly lower than background renal parenchyma.¹⁴

US has been used to detect thrombus within the renal vein (►Fig. 1) and Doppler for detecting venous thrombosis in IVC in patients with RCC has been more promising. Extension of thrombosis to IVC can be successfully assessed using both modalities.¹⁵ US imaging can be improved by using contrast-enhanced ultrasound (CEUS) through bolus-injectable microbubbles. US guidance is commonly used during partial nephrectomies or enucleation procedures, and image-guided therapies like radiofrequency ablation.

CT

Multiphasic contrast CT is the gold standard for RCC imaging. On noncontrast CT, lesions have soft tissue attenuation (20–70 Hounsfield Unit). Larger lesions have areas of necrosis. Approximately 30% demonstrate calcification.¹⁶

During the corticomedullary phase of enhancement, RCCs demonstrate variable enhancement, usually less than normal cortex. Small lesions enhance homogeneously, whereas larger lesions have irregular enhancement due to necrotic areas. Clear cell subtype shows much stronger enhancement. Corticomedullary phase is also best for assessing vascular anatomy. Intraluminal growth into venous circulation, particularly renal vein, occurs in 4 to 15% of cases. Prognosis is significantly worse with IVC involvement compared to renal vein alone.¹⁷ Nephrogenic phase (80–180 seconds) is the most sensitive phase for detecting abnormal enhancement. Excretory phase is important in assessing the collecting system anatomy especially if patient is a potential candidate for partial nephrectomy.

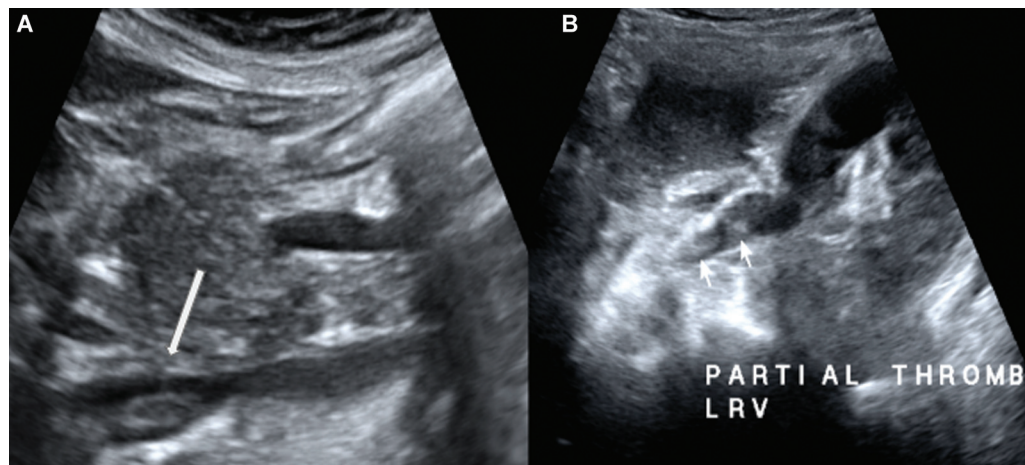


Fig. 1 Ultrasonographic images, sagittal (A) and oblique (B) sections show ill-defined thrombus in the renal vein (small white arrows) with extension to the inferior vena cava (long white arrow).

Dual-energy multidetector CT has improved the ability to differentiate clear-cell and papillary cell carcinomas, by using virtual noncontrast imaging, and iodine quantification maps.¹⁸

MRI

MRI is excellent at imaging kidneys and locally staging tumors, and also can suggest likely histology, based on T2 differences.¹⁹ Imaging features that are vital to the management decision include tumor size, tumor characterization as solid or cystic, presence or absence of macroscopic fat, tumor enhancement, and extension.

MRI protocols include T1- and T2-weighted sequences, chemical shift imaging for detection of fat, and dynamic contrast-enhanced three-dimensional (3D) gradient-echo sequences, which permit the evaluation of tumor enhancement. Multiple dynamic acquisitions are typically used to obtain corticomedullary, nephrographic, and excretory phase images. Subtraction images can help detect subtle enhancement also. A coronal 3D fast-gradient echo sequence with fat suppression after a dynamic series is useful for evaluating the renal venous anatomy and IVC for TT.²⁰

Most lesions appear heterogeneous on T1, due to areas of solid components, necrosis and hemorrhage. T2 appearance can be variable. Clear cell RCCs usually appear isointense or hypointense on T1 and heterogeneously hyperintense on T2. Clear cell RCCs being hypervascular tumors, they show prominent enhancement, especially in the corticomedullary phase, unlike other RCC subtypes. Clear cell RCCs also demonstrate rapid washout of contrast with T2 hypointensity in excretory phase. Chemical shift imaging can be useful in identifying clear cell RCC by detecting the presence of

microscopic fat.²¹ Papillary RCCs show homogeneously low signal intensity on T2 because of intratumoral hemosiderin and low levels of enhancement.

Diffusion-weighted imaging and apparent diffusion coefficient maps also enable distinguishing between malignant and benign lesions (→ Fig. 2). However, some benign pathologies also exhibit restricted diffusion, for example, chronic hemorrhagic cysts, pyelonephritis, and abscesses. Several newer MRI methods to examine perfusion properties of RCC include arterial spin-labeling, dynamic contrast enhancement-MRI, and blood-oxygenation-level-dependent-MRI.

Tumor Thrombi

Venous migration of tumor and formation of TT are unique features of RCC with significant therapeutic and prognostic implications.²² TT has been reported to occur in about 10% of patients with RCC³ Among them, 2 to 16% show extension of tumor into the right atrium. Some cases may show invasion of tumor into IVC wall, which is difficult to determine preoperatively.²³

It is vital to distinguish TT from “bland” thrombus (free of neoplastic cells), as this often impacts staging and treatment approach.²⁴ Imaging features consistent with TT on contrast-enhanced CT (CECT) and MRI include the appearance of vessel expansion, presence of enhancement, and diffusion restriction. TNM staging classifies the RCC as T3 if the tumor extends major veins; T3a if it extends into the renal vein or its segmental (muscle-containing) branches; T3b if it extends into the infra diaphragmatic IVC; and T3c if it extends into the supra diaphragmatic IVC or invades the wall of the IVC.

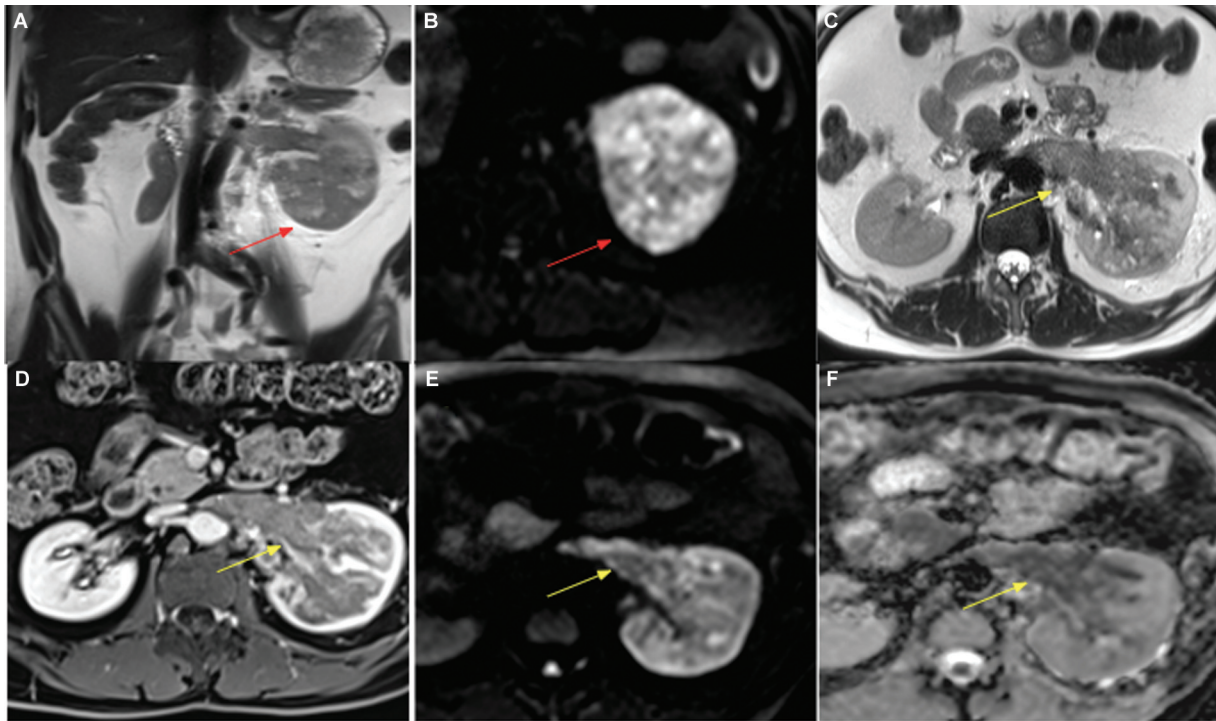


Fig. 2 MR images of 50 years old male patient: T2 coronal image (A) shows ill defined lesion in the left kidney (red arrows) with restricted diffusion in DWI (B). T2 HASTE axial (C) image shows tumour thrombus (yellow arrows) with extension to left renal vein. Post contrast T1 (D) image shows heterogeneous contrast enhancement with DWI (E) and ADC (F) images show diffusion restriction in the left renal vein thrombus.

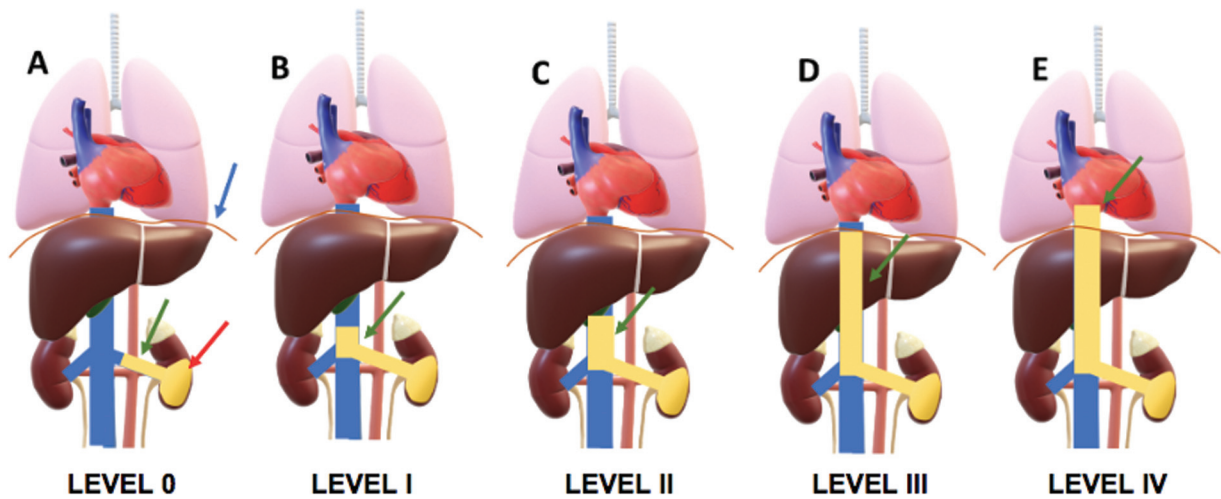


Fig. 3 Schematic representation of the Mayo Clinic thrombus classification for inferior vena cava tumor thrombus in renal cell carcinoma. (Red arrow indicating renal tumor in lower pole of left kidney, Green arrow indicating thrombus in renal vein and its extension into IVC and atrium, Blue arrow indicating Diaphragm. Tumor and thrombus were shown in yellow colour).

Major factor for characterizing the TT is the assessment of extent of thrombus. According to Mayo Clinic thrombus classification for IVC-TT in RCC,⁴ thrombus (►Fig. 3) is classified as:

- Level 0—extending to renal vein (►Fig. 4).
- Level I—extending into IVC less than or equal to 2cm above renal vein (►Fig. 5).
- Level II—extending into IVC more than 2 cm above renal vein, but not to hepatic veins (►Fig. 6).
- Level III—extending into IVC above hepatic vein but below diaphragm (►Fig. 7).
- Level IV—extending into supradiaphragmatic IVC or right atrium (►Fig. 8).

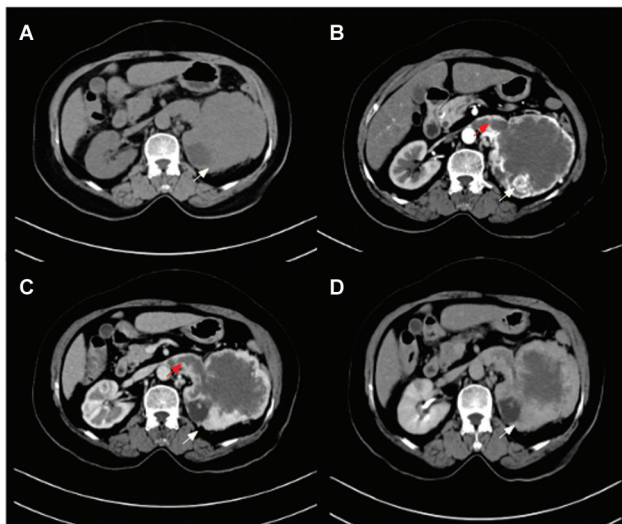


Fig. 4 Plain and contrast axial computed tomographic images show (A) Lobulated mass lesion in the left kidney (white arrows). (B) Arterial phase shows heterogeneous enhancement with tumor thrombus (red arrows) extending into left renal vein (C) and (D) venous and delayed phase images show redemonstration of thrombus, suggesting level 0 involvement.

Because of the alteration in prognosis according to the cranial extension in IVC and the related surgical complications, group III is subdivided according to the anatomical relation of thrombus to the major hepatic veins:²³

- IIIa (intrahepatic): Thrombus extending into the retrohepatic IVC but below the ostia of major hepatic veins.
- IIIb (hepatic): Thrombus extending into the retrohepatic IVC reaching the ostia of major hepatic veins; and may extend into hepatic veins causing Budd-Chiari syndrome.
- IIIc (suprahepatic, infradiaphragmatic): Thrombus extending into the retrohepatic IVC above the major hepatic veins but below the diaphragm.
- IIId (suprahepatic, supradiaphragmatic and infra-atrial): Thrombus extending into the supradiaphragmatic, intra-pericardial IVC but not into right atrium.

Additional features for the assessment of TT include evaluation of the diameter of the vessel, and vessel wall invasion, which aid in surgical planning. According to Zini et al, anteroposterior (AP) diameters of IVC and renal vein on abdominal MRI at the level of the renal vein ostium greater than 18 and 14 mm, respectively, were 90% sensitive for predicting IVC wall invasion.²⁵ Another study by Aslam Sohaib et al proposed that the most reliable sign of vessel wall invasion was a tumor signal on both the intraluminal and extraluminal sides of the IVC wall, and reported that MRI was 92% accurate in predicting vein wall invasion.²⁶

Optimal radiographic thresholds that univariately predicted the need for extensive vascular resection included a renal vein diameter at ostium of 15.5 mm, maximal diameter of IVC of 34 mm, and AP and coronal diameters of IVC at the level of ostium of 24 and 19 mm, respectively.²⁷ Presence of right-sided tumor, AP diameter of the IVC at renal ostium at least 24 mm, and radiographic evidence of complete occlusion of the IVC at the ostium were associated with a significantly increased risk of need for extensive vascular resection.

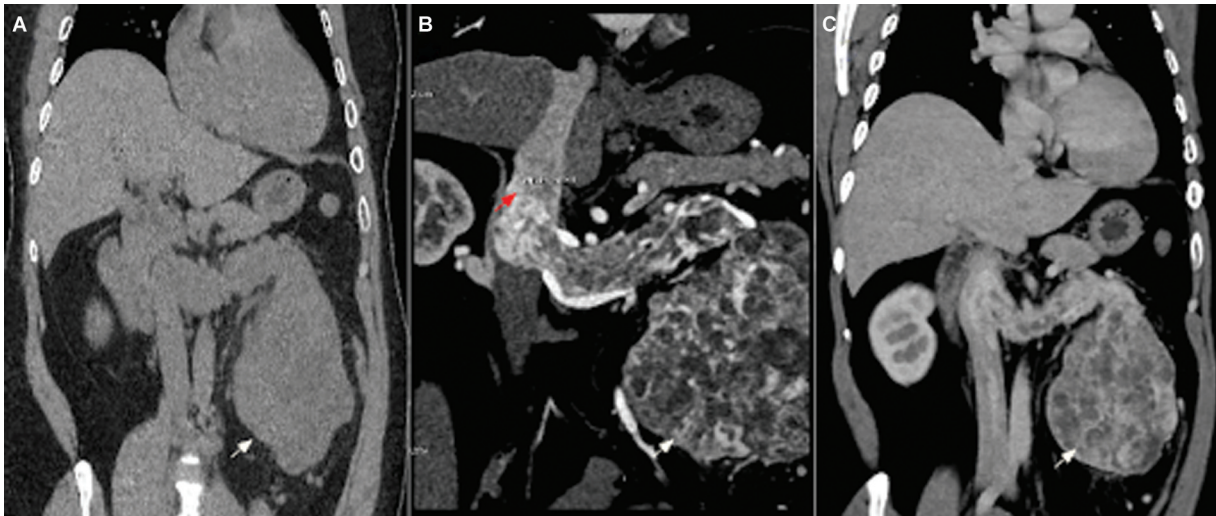


Fig. 5 Plain and contrast computed tomographic images show (A) mass lesion in the left kidney (white arrows) with heterogeneous arterial enhancement (B) and tumor thrombus (C) extending into IVC less than 2 cm (red arrow) above renal vein, suggestive of level I involvement.

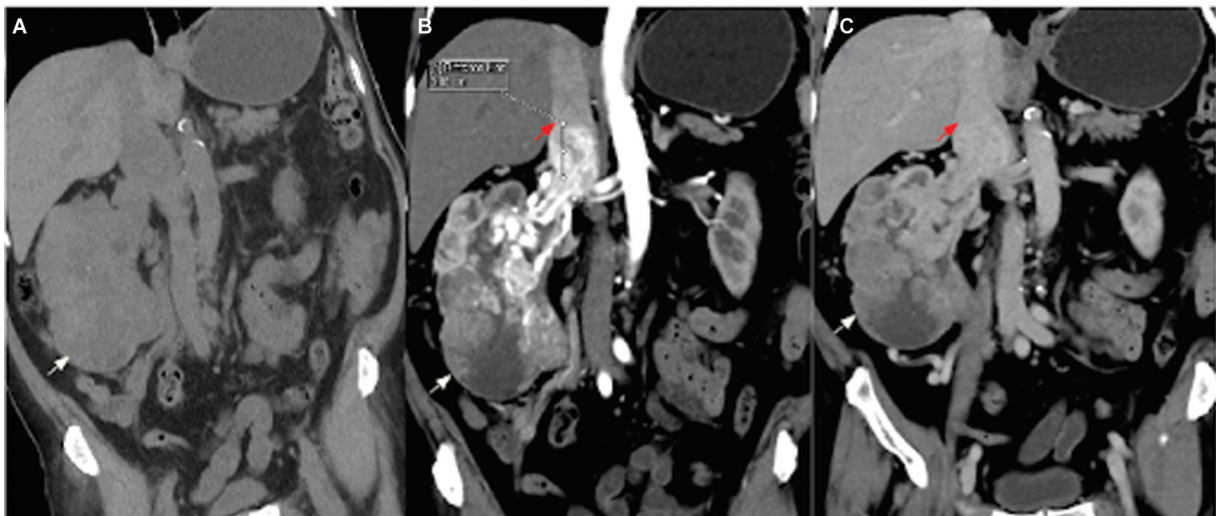


Fig. 6 Plain and contrast computed tomographic images show (A) lobulated lesion in the right kidney (white arrows) with heterogeneous arterial enhancement (B) and tumor thrombus (C) extending to more than 2 cm (red arrows) above the renal vein but below hepatic veins, suggestive of level II involvement.

Management

The aim of surgical management of RCC with IVC TT is complete resection of all tumor burden.²⁸ Preoperative IVC filter deployment is frequently avoided in surgical candidates because these devices make thrombectomy more difficult to perform and have the potential to integrate with TT.²⁹ However, individuals with persistent pulmonary embolism despite anticoagulation or those for whom anticoagulation is contraindicated can be taken up for suprarenal IVC filters.

1. Level 0 or I cases: thrombus is milked back into the renal vein and removed en bloc with the nephrectomy specimen and renal vein.
2. Level II requires mobilization of IVC and contralateral renal vein, to enable vascular control proximal and distal to thrombus.

3. Level III may additionally need mobilization of liver using liver transplant maneuvers.
4. Level IV necessitates cardiopulmonary bypass; however, veno-venous bypass may be utilized following liver mobilization, if thrombus is free floating and able to reduce below diaphragm.

Hence, imaging classification of the level of thrombus is mandatory for proper planning of surgery.

Conclusion

RCC accounts for majority of adult renal neoplasm and tumor thrombi is common in RCC, which can extend to the renal vein and IVC. The level of TT influences the surgical approach in RCC; hence, tailoring the scans to include thorax in appropriate cases is of utmost importance, as described in the article.

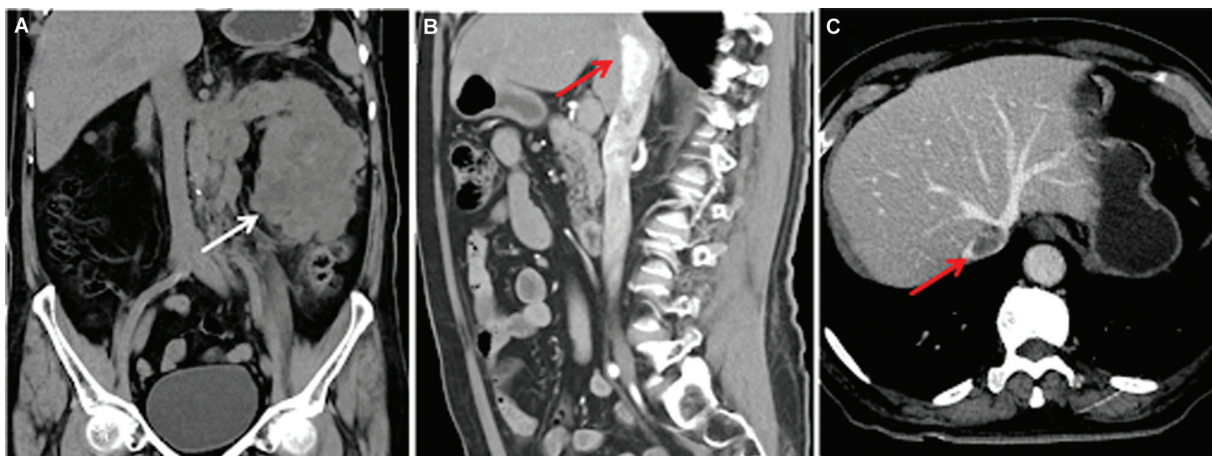


Fig. 7 Plain and contrast computed tomographic images show (A) mass lesion in the left kidney (white arrow) with tumor thrombus (B) and (C) extending above hepatic veins and below diaphragm (red arrows), suggesting level III involvement.

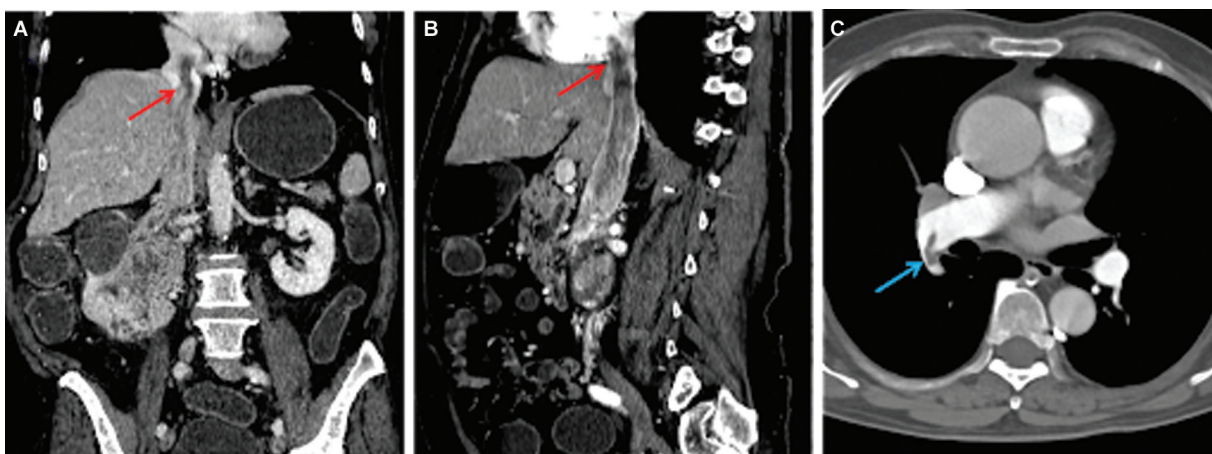


Fig. 8 Contrast computed tomographic images show (A) arterially enhancing lesion in the right kidney (white arrow) with tumor thrombus (B) into inferior vena cava with extension to right atrium (red arrow) and (C) pulmonary thrombus in right pulmonary artery (blue arrow), suggesting level IV involvement.

Teaching Points

1. RCC with extension into renal veins causes scrotal varicoceles, majority being left sided, as seen in around 11 % of men with RCC. These varicoceles typically fail to empty when the patient is recumbent.
2. Clear cell RCCs are hypervascular tumors; they show prominent enhancement, especially in the corticomedullary phase, unlike other RCC subtypes.
3. Papillary RCCs show homogeneously low signal intensity on T2 because of intratumoral hemosiderin and low levels of enhancement.
4. Imaging features consistent with TT on CECT and MRI include the appearance of vessel expansion, presence of enhancement, and diffusion restriction.
5. The most reliable sign of vessel wall invasion was a tumor signal on both the intraluminal and extraluminal sides of the IVC wall, and reported that MRI was 92% accurate in predicting vein wall invasion.

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Conflict of Interest

None declared.

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