Utility of ultrasonography in preoperative assessment of tumor thrombi in kidney cancer

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Introduction: *This study examined the clinical accuracy of ultrasonography compared to magnetic resonance imaging (MRI) and intraoperative findings for evaluation of tumor thrombi level in patients with renal cell carcinoma.*

Materials and methods: *We retrospectively identified 38 patients at our institution who underwent both ultrasonography and MRI before undergoing open radical nephrectomy with tumor thrombectomy between 2010 and 2019. We compared tumor thrombus level findings of both ultrasonography and MRI, as well as the diagnostic accuracy of each to intraoperative findings. Agreement between ultrasonography, MRI, and surgery was tested with kappa. Logistic regression models identified factors that predict a mismatched thrombus level between an imaging modality and surgical findings.*

Results and Conclusions: *Tumor thrombus levels determined by ultrasonography matched with MRI in 26 (68.4%) cases. Compared to operative findings, ultrasonography accurately identified the cephalad extent of thrombi in 30 (79.0%) cases, under-staged five (13.2%) cases, and over-staged three (7.9%). Magnetic resonance imaging agreed with operative findings in 30 (79.0%) cases, under-staged five (13.2%) and over-staged three (7.9%) cases. On univariable regression assessment, M1 stage was predictive of a mismatched result between MRI and surgery (OR: 6.0, 95% CI: 1.02-35.3, p = 0.047), but this association did not hold-up in a multivariable model. Ultrasonography and magnetic resonance imaging identified the preoperative tumor thrombus level at a rate of 79%. Ultrasonography is an effective preoperative imaging modality for evaluating tumor thrombi associated with kidney cancer, notably as an adjunct to magnetic resonance imaging.*

Key Words: ultrasonography, vena cava, inferior, carcinoma, renal cell, thrombosis, magnetic resonance imaging

Introduction

Globally, kidney cancer represents 2.2% of all malignancies and was responsible for 175,098 deaths in 2018.[1] In 2019, the United States reported 73,820 new cases and 14,770 deaths from this disease.[2] Kidney cancers harbor the potential to form a tumor thrombus (TT) that can invade into the renal vein, through the inferior vena cava (IVC), and extend cephalad, even to the heart. Tumor thrombi are observed in 4%-10% of all kidney cancer cases,[3] but are reported in as high as 20% of patients seen at tertiary referral centers.[4,5] Surgical resection of primary malignancy with IVC tumor thrombectomy is the gold standard treatment for these patients, significantly improving survival outcomes.[6] Extirpative surgery with tumor thrombectomy and negative surgical margins can be curative for non-metastatic renal cell carcinoma (RCC)

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patients with TT.[7] Contrarily, this population faces a median survival period of 8 months without any therapeutic intervention.[8]

Radical nephrectomy with IVC thrombectomy requires extensive surgical planning. Given their complexity, most surgical cases are performed at major referral centers by a limited number of experienced surgeons.[6,9,10] The cephalad extent of the TT should be evaluated preoperatively, as it influences the approach of the surgical incision and anticipates the need for any special surgical maneuvers or involvement of other surgical subspecialties. Higher level thrombi may require preparation for hepatic mobilization and cardiac bypass. A thrombus that invades the caval wall may require IVC resection and/or reconstruction. The distance of the TT from the confluence of the hepatic veins determines whether to clamp above or below the major hepatic veins. If the surgeon clamps above the hepatic veins, the porta hepatis is clamped in the Pringle maneuver to lessen hemorrhage. Complete hepatic vascular occlusion increases risk for ischemic hepatic injury and splenic engorgement. Precise knowledge of thrombus level is required to provide an accurate informed consent process describing specific risks and benefits of the procedure associated with the specific TT level.[6,9,10]

Magnetic resonance imaging (MRI) is widely accepted as the imaging method of choice for preoperative TT staging.[6,11] However, ultrasonography may be used as an additive decisional tool in patients requiring repeat imaging from initial MRI to time of surgery. Limited studies have assessed the accuracy of ultrasonography in determining TT levels preoperatively, with favorable findings. The purpose of this study is to understand the accuracy of ultrasonography compared to MRI and intraoperative findings in evaluating TT extent.

Materials and methods

We retrospectively identified 48 patients who underwent both IVC ultrasonography and MRI preoperatively before undergoing an open radical nephrectomy with IVC tumor thrombectomy at our tertiary care institution between 2010 and 2019. Institutional review board approval was obtained. Four patients were excluded because the quality of their imaging studies was not adequate for review. The final cohort consisted of 38 patients, Figure 1.

Regarding ultrasonography studies, 31 cases were performed in a point-of-care setting in the urology clinic by an ultrasound technician with 17 years of experience in general ultrasonography and 3 years in urologic ultrasonography. All 31 cases were reviewed by an attending urologic oncologist with > 15 years of experience managing patients with RCC associated with IVC TT. The remaining seven cases were performed in the radiology department by ultrasonography technicians of varying levels of experience and reviewed by various attending radiologists. Regarding MRI studies, 36 cases were performed in the radiology department at our institution and reviewed by attending radiologists of varying levels of experience. The remaining two cases were performed at outside institutions. The radiologists' expertise level at these outside institutions could not be ascertained.

We extracted data regarding the proximal extent of the TT from ultrasonography and MRI reports. We used the Neves classification of vena cava thrombi levels as our reference standard, Table 1.[4]

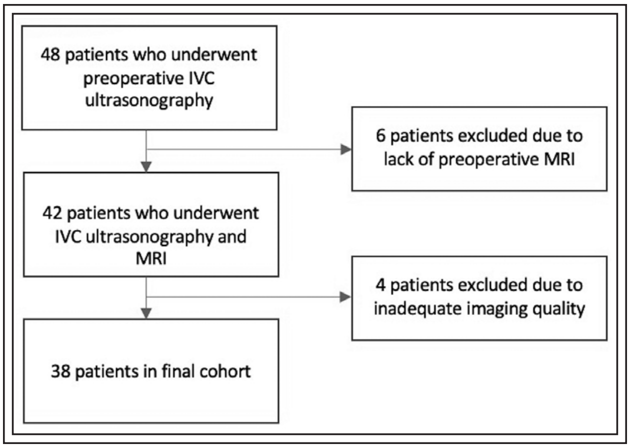

Figure 1. Depicts which patients were included and excluded from the final cohort.

TABLE 1. **Neves tumor thrombus classification**

Level	Description
0	At the level of the RV
1	In the IVC < 2 cm above the RV
2	In the IVC > 2 cm above the RV
3	Above the hepatic veins and below the diaphragm
4	Above the diaphragm

RV = renal vein; IVC = inferior vena cava

We compared ultrasonography findings against MRI findings to determine agreement between ultrasonography and MRI, then analyzed the sensitivity and specificity of both imaging modalities against intraoperative findings, the gold standard. Agreement between ultrasonography, MRI, and surgery was tested with kappa. After assessment for confounders and interaction, we constructed separate univariable and multivariable logistic regression models for MRI and ultrasonography to identify factors that can predict a mis-matched thrombus level between an imaging modality and surgery. SAS 9.4 (Cary, NC, USA) was used for statistical analyses. Significance was set at two-sided alpha of 0.05. In certain cases, clinical and operative notes were reviewed to assess the impact of imagining findings on surgical management.

At our institution, the following protocol was followed for performing ultrasonography for IVC TT. If possible, the patients were asked to fast 6 to 8 hours before the procedure to decrease potential obscuration from gastrointestinal contents. First, sagittal images of the IVC were obtained in the supine position. A curved array probe was positioned at the midline of the abdomen underneath the xiphoid process and moved slowly inferiorly until the IVC, right atrium, and the confluence of the hepatic veins were identified. The standard frequency used was 3.5 megahertz, which could be adjusted down to 2.5 megahertz on larger patients and up to 7.0 megahertz on thinner patients to improve image quality. Typically, higher level thrombi were better visualized in the sagittal plane, but a transverse view of the IVC could also be obtained. If still without a clear view of the IVC, the patient was examined in the lateral decubitus position. Often, this was the optimal position for lower-level thrombi and obese patients.

Results

The age range of patients in our cohort was 24 to 77 with the mean age at the time of surgery of 60.6 years (SD ± 12.51). Average body mass index (BMI) was 27.53 kg/m^2 (range: 16.80-38.60). Twenty-eight patients had primary tumors in the right kidney; ten in the left. Of the 38 cases, 37 were RCCs divided into the following subtypes: 31 clear cell, three unclassified, two papillary, and one collecting duct. One patient had an epithelioid angiomyolipoma. Surgical pathology classified four patients with pT3a tumors, 13 with pT3b, 18 with pT3c, and two with pT4.

The mean time between ultrasonography and surgery was 17.84 days (range: 1-43). The mean time between MRI and surgery was 20.50 days (range: 1-59). Of 38 patients, 32 had both ultrasonography and MRI performed within 30 days of their operation. In our total cohort, 12 ultrasonography and 15 MRI studies were performed within this timeframe.

We first compared ultrasonography findings to MRI findings, finding that TT levels matched in 26/38 (68.4%) cases between these two imaging modalities. When compared to MRI, ultrasonography under-estimated the level of TT in five (13.2%) patients and over-estimated in seven (18.4%). We then compared ultrasonography and MRI to operative findings as the ultimate gold-standard, finding that both modalities agreed with operative findings in 30/38 (79.0%) cases. Ultrasonography accurately identified the cephalad extent of TT in 30 (79.0%) cases, underestimated five (13.2%) cases (three by one TT level, two by two TT levels) and over-estimated three (7.9%) cases (two by one TT level, one by two TT levels). An example of an accurate ultrasonography study can be seen in Figure 2.

MRI also agreed with surgical findings in 30 (79.0%) cases, under-estimated five (13.2%) cases by one TT level and over-estimated three (7.9%) cases by one TT level. MRI never under- or over-estimated cases by more than one TT level. Figure 3 portrays an MRI image that underestimated the TT level.

Although both MRI and ultrasonography correctly predicted TT levels in 30/38 cases, the cases under- or over-estimated by ultrasonography were not the same ones under- or over-estimated by MRI.

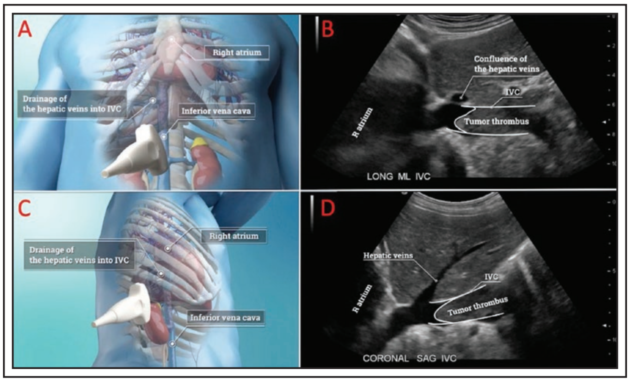

Figure 2. (A) Schematic view of IVC tumor thrombus in sagittal plane. **(B)** Gray scale US image in the sagittal plane demonstrates IVC tumor thrombus and its relationship to hepatic veins, right atrium. **(C)** Schematic view of IVC tumor thrombus in coronal plane. **(D)** Gray scale US image in the coronal plane demonstrates IVC tumor thrombus and its relationship to hepatic vein, right atrium. IVC = inferior vena cava; US = ultrasonography.

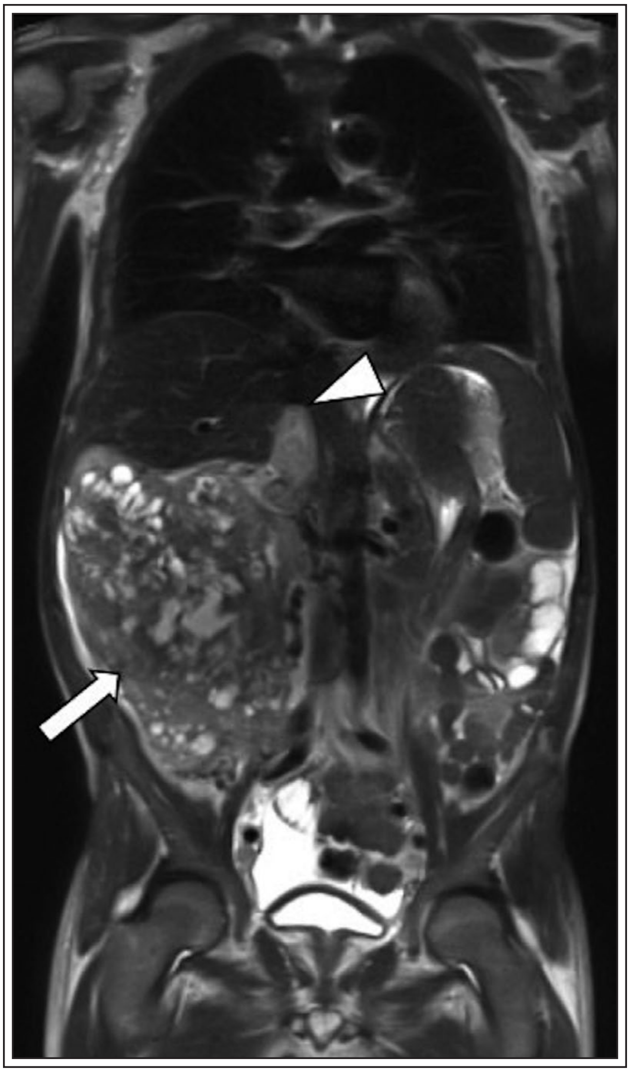

Figure 3. Coronal T2-weighted magnetic resonance image of chest, abdomen, and pelvis demonstrates a large, heterogeneous right renal mass **(white arrow)** with tumor extension into right renal vein and inferior vena cava **(arrowhead)**. Cranial extent of tumor was reported as a level 2 thrombus but was found to be a level 3 thrombus.

Amongst the eight cases incorrectly staged by ultrasonography, the average BMI was 28.76 kg/m^2 (27.21 kg/m^2 for cases correctly staged by ultrasonography). Six had primary tumors in the right and two in the left. Seven had clear cell subtype RCC. One had papillary RCC. The average time to surgery from ultrasonography was 21.25 days for under- and over-diagnosed cases (16.93 days for correctly staged ultrasonography cases). For the eight cases incorrectly staged by MRI, the average BMI was 24.98 kg/m^2 (28.22 kg/m^2 for cases correctly staged by MRI). Six had primary tumors in the right and two in the left. Seven had clear cell subtype RCC. One had papillary RCC. The average time from MRI to surgery was 14.50 days for incorrectly staged cases (22.10 days for correctly staged MRI cases).

Regarding higher level tumor thrombi, ultrasonography correctly identified the level of 3 of the 4 level III thrombi and 1 of the 2 level IV thrombi. One level III thrombus was under-staged by one level. One level IV thrombus was under-staged by 2 levels. MRI correctly staged the level of 1 of the 4 level III thrombi and all of the level IV thrombi. Of the three level III thrombi cases inaccurately staged by MRI, two were under-staged by one TT level; one was over-staged by one TT level. Our findings are further delineated in Tables 2 and 3.

The univariable logistic regression did not find any demographic or tumor characteristic predictive of a mis-matched result between ultrasonography and surgery, while a multivariable model did not converge. On univariable regression assessment, M1-stage was predictive of a mis-matched result between MRI and surgery (OR: 6.0, 95%CI: 1.02-35.3, $p = 0.047$), but this association did not hold-up in a multivariable model adjusting for other characteristics.

Discussion

Our results demonstrate that ultrasonography is comparable to MRI in accurately determining the cephalad extent of tumor thrombi in kidney cancer patients. In our institutional cohort, both ultrasonography and MRI agreed with surgical findings at a frequency of 79.0% (30/38).

Of interest were the Neves level III and IV thrombi that extend beyond the hepatic venous confluence and into the right atrium, respectively. Such higher-level thrombi significantly increase the risk of operative morbidity and the complexity of surgical planning. With thrombi above the hepatic veins, the porta hepatis is often clamped to minimize blood loss. This maneuver increases the risk for ischemic hepatic injury, portal vein thrombosis, and splenic engorgement and rupture.[12] Additionally, at our institution, levels III and IV TT procedures are performed in cardiac operating rooms in anticipation of possible cardiothoracic surgery involvement with bypass techniques. Bypass complicates the clinical picture by increasing the risk of coagulopathies, intraoperative events, longer operative time, and extended hospital stay. Precise knowledge of the TT level also improves the procedure's informed consent process as different TT levels may be associated with varying risk levels,

TABLE 2. **Staging by surgery, US, MRI**

IVC TT level	Surgical findings	US findings	MRI findings
0	2 (5.26%)	3 (7.89%)	1 (2.63%)
I	9 (23.68%)	8 (21.05%)	11 (28.95%)
II	21 (55.26%)	22 (57.89%)	21 (55.26%)
III	4 (10.53%)	4 (10.53%)	2 (5.26%)
IV	2 (5.26%)	1 (2.63%)	3 (7.89%)

IVC = inferior vena cava; TT = tumor thrombus; US = ultrasonography; MRI = magnetic resonance imaging; TT = tumor thrombus; MRI = magnetic resonance imaging

complication rates, and outcomes.[4,13] Although our cohort size was too small to determine statistical significance, ultrasonography correctly staged four and MRI correctly staged three of six total level III and IV thrombi.

Tumor thrombi have an inclination for rapid progression. Current literature recommends that preoperative imaging should be obtained within 1 to 2 weeks of surgery.[4,9,14] Woodruff et al delineates a cutoff of 'not past 30 days'.[15] In our cohort of 38 patients, three ultrasonography studies and six MRIs were performed outside 30 days of surgery. Out of these three ultrasonography cases, two images were in agreement with surgical findings; one under-estimated the extent of the TT as level zero, while surgical pathology reported it as a level II thrombus. Notably, average time from ultrasonography to surgery was greater in correctly staged cases (16.93 days) compared to incorrectly staged cases (21.25 days). Although our cohort size was too small to perform a statistical analysis, this timeframe may have contributed to under-staging. This was not the case with MRI; time from imaging to surgery was greater for incorrectly (22.10 days) versus correctly (14.5 days) staged cases.

TABLE 3. **Underestimated, over-estimated cases by modality**

	Ultrasonography: TT level	Surgery: TT level	ΔTT level
Case 2	II	III	+1
Case 21	0	I	+1
Case 24	III	II	-1
Case 29	0	I	+1
Case 30	II	0	-2
Case 32	II	IV	+2
Case 35	I	0	-1
Case 38	0	II	+2
	MRI: TT level	**Surgery: TT level**	**ΔTT level**
Case 2	II	III	+1
Case 8	II	III	+1
Case 11	III	II	-1
Case 16	I	II	+1
Case 18	II	I	-1
Case 28	IV	III	-1
Case 34	I	II	+1
Case 35	I	0	-1

TT = tumor thrombus

While a discrepancy of one TT level may be inconsequential amongst level I or II thrombi, misinterpretation of two TT levels may significantly alter the clinical course. We reviewed the course of three cases in which ultrasonography mis-staged TT by two levels. For case 30, the ultrasonographer noted that findings were limited by the presence of bowel gas and a large body habitus. Thus, MRI findings were primarily utilized for clinical decision making. For cases 32 and 38, MRI was obtained after ultrasonography and was therefore utilized as the most recent source of imaging. While these findings reflect the limitations of ultrasonography use in this population, we found that no significant changes to surgical approach or disease management were identified in our cohort. The combinative benefit of ultrasonography and MRI and the role of ultrasonography as an adjunct, rather than a replacement for MRI, is highlighted here.

Similar studies comparing ultrasonography to different imaging modalities for preoperative tumor staging in patients with TT associated with RCC have been conducted with variable findings, Table 4.

TABLE 4. **Studies evaluating ultrasonography versus MRI in assessing IVC tumor thrombus level**

Study	**Nabavizadeh, Lee et al (2020)**					**Guo et al**					**Kallman et al**			
TT category	**Neves**					**Neves**					**Distal RV**	**Subhepatic IVC**	**Intrahepatic IVC**	**R Atrium**
TT level	0	I	II	III	IV	0	I	II	III	IV				
US														
Correct	0	7	19	3	1		3	6	4	5	3	4	6	
Under		2	1	1	1		3	1			4	2		
Over	2		1					2	1					
Total	2	9	21	4	2	0	6	9	5	5	7	6	6	0
MRI														
Correct	1	8	18	1	2		6	9	5	3	1	1	1	2
Under			2	2						2		1		
Over	1	1	1	1										
Total	2	9	21	4	2	0	6	9	5	5	1	2	1	2

MRI = magnetic resonance imaging; IVC = inferior vena cava; TT = tumor thrombus; RV = renal vein; US = ultrasonography

Kallman et al[16] and Guo et al[17] report lower diagnostic accuracy for ultrasonography compared to MRI. Of note, both studies demonstrated excellent diagnostic accuracy for higher level thrombi. Corroborating our findings, studies by Bos et al,[18] Gupta et al,[19] and Habboub et al[20] report comparable diagnostic accuracy for ultrasonography compared to other imaging modalities including MRI and multidetector computed tomography (MDCT), which literature indicates is a comparable alternative to MRI for TT staging.[21,22] Additionally, similar studies have been performed investigating the role of intraoperative transesophageal echocardiography for tumor thrombi associated with kidney cancer. While an intraoperative exam does not provide information for surgical planning and patient counseling in advance to the start of operation, the benefits of assessing TT level in in real-time have been reported in literature, especially in patients with higher level thrombi and high risk of embolization.[23,24]

Another important benefit of ultrasonography not examined in this study is its unique ability to detect tumor mobility, using the surrogate marker of flow around the thrombus, informing the surgeon if the thrombus can be manipulated below critical structures such as the hepatic vein confluence or the cavoatrial junction.[25] Milking the thrombus below such thresholds may eliminate the need for more invasive surgical procedures such as hepatic mobilization, thoracotomy, pericardial window, and cardiac bypass.[26]

Of practical significance, MRI is often obtained at the time of diagnosis to understand the renal vascular anatomy, identify local extension and/or metastasis, and characterize tumor extent.[10] Once diagnosed, patients are often referred to a specialist at a major referral center who performs radical nephrectomies with IVC thrombectomy and possible vascular reconstruction. This often amounts to greater than the recommended 2-week timeframe within which preoperative imaging should be obtained.[4,9,14] A portion of patients need to be re-imaged to capture the precise extent of the TT prior to the procedure. In the era of value-based care, ultrasonography is more affordable and accessible than MRI. Ultrasonography lacks some drawbacks of obtaining a repeat MRI within a 2-week timeframe, including wait time, possible need for insurance approval, incompatibility with some implanted devices, claustrophobia in some patients, and the need for intravenous contrast. Ultrasonography may be beneficial in this specific setting as an adjunct to MRI.

While this is the largest study directly comparing ultrasonography to MRI for caval tumor thrombi, there are several limitations, including: relatively small cohort size (n = 38), a single-institution population, and retrospective study design. Moreover, the mean time between imaging and surgery was longer than the recommended 2-week timeframe in our population; the TT may have progressed in this interim. Nevertheless, the mean duration between ultrasonography and surgery was similar to the mean duration between MRI and surgery. Finally, the original ultrasonography studies were performed by technicians with differing levels of expertise. This points to a significant limitation of ultrasonography imaging, being heavily dependent on the experience of the ultrasonographer. Further, the ultrasonography exam may be limited by body habitus or the presence of abdominal gas. Additional limitations reported in literature include its dependence on the position of the thrombus. However, low sensitivity has been reported for thrombi below the hepatic vein,[27] which does not significantly impact surgical management. Future studies that are multi-institutional, prospective in design, and of larger cohorts are encouraged to further validate the use of ultrasonography as an adjunct to MRI for preoperative staging and surgical planning in this rare subset of patients. Additionally, further studies are required to understand the role of ultrasonography in assessing TT mobility. Finally, further research is needed to determine the optimal patient population for ultrasonography considering factors such as BMI.

Conclusion

This study investigated the clinical accuracy of ultrasonography compared to MRI and intraoperative findings in detecting the cephalad extent of thrombi in patients with RCC associated with TT. At our institution, we found that both ultrasonography and MRI agreed with surgical findings at a rate of 79%. Ultrasonography is an affordable, reliable, and quick test that can function as an additive decisional tool for surgical planning and disease management in patients requiring repeat imaging prior to surgery after initial MRI/MDCT workup. Our 3D animation demonstrates the ultrasonography technique for detection of caval TT. ☐

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