

Contrast-Enhanced Ultrasound for Intraoperative Tumor Contour Definition During Complex Partial Nephrectomy

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Abstract: Contrast-enhanced ultrasound (CEUS) is an imaging modality that utilizes a non-nephrotoxic, intravascular microbubble agent to capture real-time perfusion of the target organ. CEUS has demonstrated utility for the evaluation and surveillance of indeterminate renal lesions in patients who are unable to receive conventional contrast agents, yet its potential utility in renal surgery remains poorly defined in the current literature. We present a series of 4 patients who underwent successful intraoperative CEUS during partial nephrectomy (PN) to help define renal mass contour and proximity to vascular structures in an attempt to optimize renal function after PN. All cases were endophytic with moderate-high complexity (R.E.N.A.L. scores >9). CEUS was safely performed in all cases providing excellent tumor contour definition. In one case, CEUS provided better visualization of tumor proximity within the hilum than conventional US, facilitating surgical resection and reconstruction. In another case, CEUS provided better definition of tumor contour, allowing wedge resection rather than heminephrectomy. Margins were negative in all cases. The average global renal function preserved following PN was 90%. While grey-scale US with color Doppler is usually sufficient for intraoperative tumor visualization, CEUS can be considered during PN for complex endophytic, infiltrative or hilar tumors where accurate delineation of tumor contour is critical.

Keywords: Contrast-enhanced Ultrasound, Kidney Neoplasms, Nephron-sparing Surgery, Functional Outcomes

1. Introduction

Standard grey-scale ultrasound (US) with Doppler is often utilized intraoperatively during PN to confirm tumor location and proximity to key structures prior to resection [1-3]. US is relatively quick, safe, and cost-effective for intraoperative use. Occasionally, endophytic, infiltrative, or hilar tumors remain difficult to visualize with conventional US, leading to a larger proportion of healthy parenchyma being removed in order to ensure an acceptable oncologic margin.

Contrast-enhanced ultrasound (CEUS) has several unique characteristics that separate it from other imaging modalities of the upper urinary tract. As compared to iodinated contrast-agents used in computed tomography (CT), CEUS's unique microbubble contrast agent carries no risk of nephrotoxicity [4]. Magnetic resonance imaging (MRI) has

become more widely used in patients with chronic kidney disease (CKD) due to the low risk of nephrogenic systemic fibrosis with second-generation gadolinium-based contrast agents. However, MRI remains expensive and can have potential contraindications. CEUS is more cost-effective than MRI and similarly does not require ionizing radiation [5-7]. Compared to CT/MRI, CEUS has comparable sensitivity, specificity, and positive and negative predictive value when evaluating indeterminate renal lesions and it provides reliable assessment of whether the lesion enhances [8, 9]. Thus, CEUS is primarily being utilized by urologists in select patients with CKD for surveillance of indeterminate solid or complex-cystic renal lesions [8, 10].

There is emerging evidence that CEUS may also have intraoperative applications. Specifically, CEUS has been shown to improve tumor characterization and alter surgical management in patients with hepatic tumors [11]. Within

urology the role of intraoperative CEUS during renal surgery has not been well studied, with only two series reported to date [12, 13]. We present a retrospective review of four cases of partial nephrectomy (PN) where intraoperative CEUS was employed to inform surgical management of complex renal lesions.

2. Surgical Approach

All 4 patients underwent open PN via a flank incision at a single tertiary-care facility (Table 1). Our radiologists performed standard grey-scale US with color-Doppler

followed by CEUS using a GE L3-9i linear-transducer with a GE-Logiq-S8 ultrasound machine. For CEUS, 2.5 ml of microbubble contrast-agent (Lumason, Bracco-Diagnostics) was administered intravenously, and renal images were recorded continuously in real-time for approximately 60-120 seconds, allowing visualization of both cortical and subsequent medullary phases of enhancement. Once the tumor was clearly identified, the renal arteries and veins were clamped, and hypothermia was applied. The kidney was incised sharply to remove the tumor and renorrhaphy was performed in two layers. There were no intraoperative or postoperative complications.

Table 1. Patient Characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4
Patient/Tumor Characteristics				
Age (Years)	60	76	63	70
Gender	M	M	F	M
BMI (kg/m ²)	23	46	25	29
Preoperative TKI ^a	No	Yes (Axitinib)	No	Yes (Axitinib)
Tumor Size (cm) ^b	2.0	3.9	2.7	3.7
Percent Endophytic ^b	100%	100%	90%	100%
R.E.N.A.L Score ^b	9p	10x, near hilum	9a, hilar	9a, near hilum
EBL (cc)	150	200	500	250
Histology	papillary RCC	clear cell RCC	clear cell RCC	clear cell RCC
T Stage/Grade	pT1a, G2	pT1a, G2	pT1a, G3	pT1a ^c
Margin	negative	negative	negative	negative
Postoperative Complications	none	none	none	none
Functional Considerations				
Solitary Kidney (Y/N)	N	N ^d	Y	Y
Preoperative CKD stage	2	2	1	3A
Preop. SCr (eGFR) ^e	1.04 (77)	1.15 (61)	0.67 (94)	1.45 (51)
Cold Ischemia Time (minutes)	27	44	33	33
Postoperative AKI ^f	N	N	N	N
New Baseline SCr at 1-6 Months				
Postop (eGFR)	1.04 (77)	1.30 (54)	0.73 (86)	1.67 (40)
Estimated% GFR Preserved	100%	89%	91%	78%

^a8 week course of tyrosine kinase inhibitor (TKI) axitinib used to downsize the tumor to facilitate PN

^bValues listed based on imaging obtained after TKI therapy, if given

^cISUP grade unable to be determined due to extensive tissue reaction, presumed due to TKI

^dPatient presented with bilateral tumors and initially underwent right PN. The index case (left PN) was then performed 4 months later after 8 weeks of TKI to downsize the left renal tumor

^eSerum creatinine values listed in units of mg/dL and eGFR calculated utilizing MDRD equation, in units of ml/min/1.73m²

^fAKI defined in standard manner as a 1.5x rise from the pre-operative serum creatinine.

3. Case Presentations

Patient 1 presented with an incidentally-discovered endophytic right lower pole renal mass abutting the renal sinus. Conventional intraoperative US showed that the mass was irregular medially suggesting possible infiltrative disease, and heminephrectomy was under consideration. However, utilizing CEUS, the microvasculature within the tumor progressively enhanced, allowing the lesion to be clearly delineated from the normal parenchyma. Wedge resection was readily performed and negative margins were obtained.

Patient 2 is a morbidly obese male with a history of pulmonary embolism and prior right PN for renal cell carcinoma (RCC) who presented with a 4.5 cm, centrally-located left renal mass. Neoadjuvant tyrosine kinase

inhibitor (TKI) was given for eight weeks to downsize the tumor and optimize PN. TKI and anticoagulation were held 3 days prior to left PN. Using intraoperative CEUS, the borders of the tumor were more readily identified and wedge resection away from the hilum was performed without issue.

Patient 3 had bilateral ureteropelvic junction obstruction and a functionally solitary right kidney. She also presented with an enhancing, solid right renal mass abutting the central sinus and collecting system (Figures 1A/1B). Renal mass biopsy revealed eosinophilic RCC. Following brisk, early enhancement during CEUS, the margins of the tumor were identified and were noted to be more hilar than appreciated on preoperative CT or conventional US (Figures 1C/1D). Wedge resection of the tumor was performed with enucleation away from the hilar structures medially, and negative margins were obtained.

Patient 4 presented with functionally solitary kidney and a 4.7-cm upper pole mass abutting the sinus without gross collecting system or renal vein invasion. Biopsy revealed clear cell RCC. Following neoadjuvant TKI therapy, the mass decreased in size from 4.7 cm to 3.7 cm (Figures

2A/2B). Intraoperative CEUS demonstrated a well-circumscribed mass, which was hypoenhancing relative to the renal cortex, likely due to TKI effect (Figure 2C). Wedge resection was performed with negative margins.

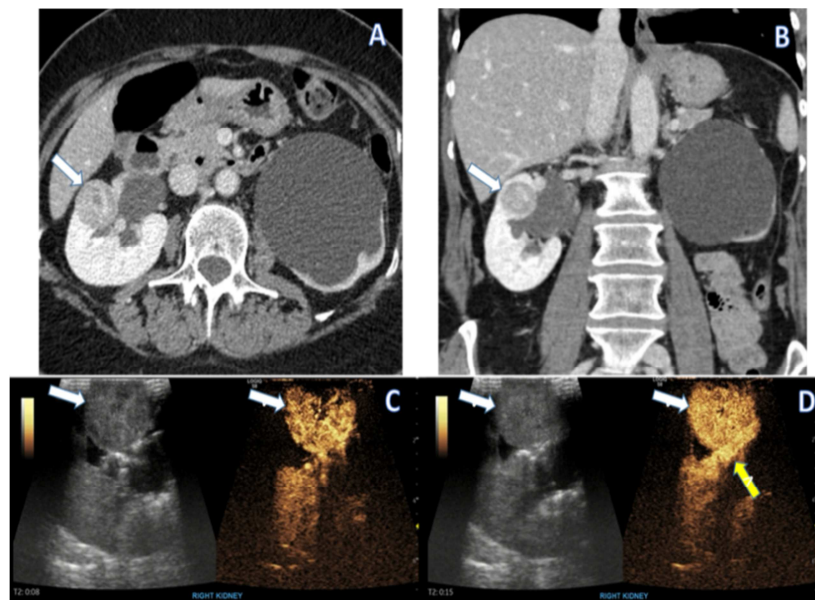


Figure 1. Preoperative CT Urogram (A) and (B) for patient 3 demonstrating a 2.7-cm solid, enhancing interpolar right renal mass (white arrow) on axial and coronal views respectively. (C) Split screen view of the right kidney with conventional ultrasound imaging on the left and CEUS images on the right with images taken in the cortical phase. Note the mass (white arrows) is hyperenhancing relative to the surrounding cortex. (D) Split screen view with transverse images taken in the early medullary phase. Note enhancement of the renal vein just posterior and medial to the tumor (yellow arrow), helping delineate the tumor's close proximity to the hilum. On conventional imaging this region appeared to be normal renal parenchyma rather than renal vein. A video showing real time CEUS for this case is also available (MP4 video attached).

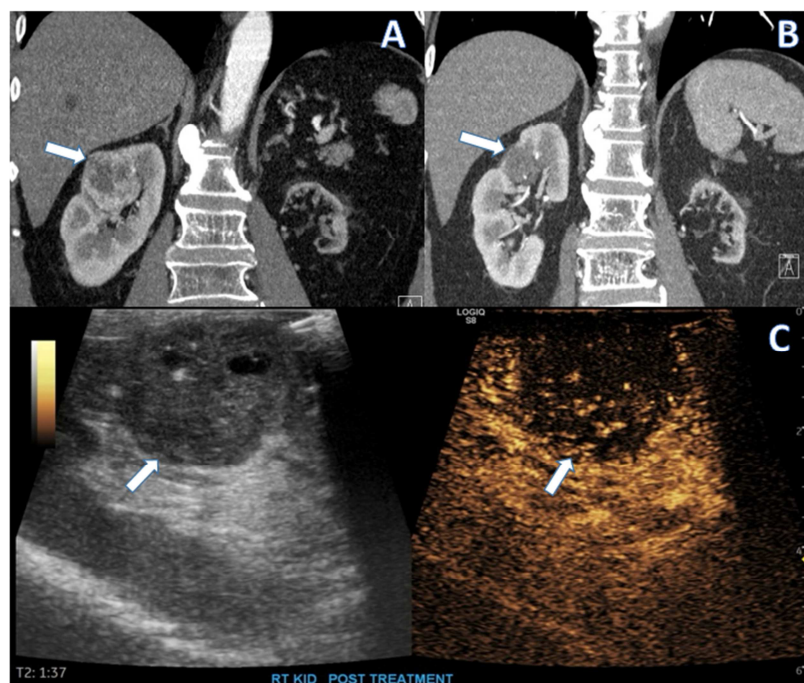


Figure 2. Preoperative CT (A, B) for patient 4 before and after TKI therapy, respectively. (A) Pre-TKI scan demonstrating a 4.7-cm heterogeneous, avidly enhancing right upper pole mass with extension into the renal sinus (white arrow). The contralateral kidney is markedly atrophic. (B) Post-TKI scan showing a decrease in size (now 3.7cm) and decreased enhancement, indicating a positive response to TKI therapy. (C) Split screen view with conventional US imaging on the left and CEUS images on the right. CEUS images were taken in the medullary phase. Here the mass (white arrow) is hypoenhancing relative to the surrounding cortex reflecting reduced vascularity related to TKI therapy.

4. Discussion

In our series, intraoperative CEUS was safely and successfully performed in 4 patients undergoing complex PN. The use of intraoperative CEUS allowed for precise delineation of tumor borders relative to critical anatomic structures such as the renal sinus and/or hilar vessels. While CEUS did not significantly alter surgical management in some of our cases, our experience was that it facilitated optimal nephron-sparing surgery with strong functional outcomes observed in all instances (Table 1). Specifically, in our 2 patients with a solitary kidney we saved 78 and 91% of the renal function and in 2 patients with a normal contralateral kidney we saved 89 and 100% of the global function. These results are favorable given that we save an average of 80% and 90% of the global renal function in patients with a solitary or contralateral kidney, respectively, and all four of our cases were relatively high complexity relative to the typical PN in our previous studies [14].

Currently, there is a paucity of evidence regarding the role of intraoperative CEUS use during renal surgery [3, 12, 13, 15]. Le and colleagues sought to examine the feasibility of intraoperative CEUS for 10 patients undergoing open PN, and reported that intraoperative CEUS was safe and feasible, only adding about 5-10 minutes of additional operative time to the procedure, like our experience [12]. The authors reported that for 6 of 10 patients CEUS demonstrated “improved lesion conspicuity, contrast, and vascularity”, but they did not believe CEUS altered surgical management in any of the cases in their series. The CEUS images in their study do not appear to be as clear and distinct as they were in our experience, and the authors remarked that imaging quality was dependent on the ultrasound probe utilized, with higher quality images obtained using a linear probe, which was utilized in our study. Differences in patient populations and tumor complexity may have also impacted perspectives about the potential added value of CEUS over standard US.

Within minimally invasive renal surgery, Rao et al demonstrated a novel use of CEUS to assess feasibility of zero-ischemia robotic-assisted partial nephrectomy by confirming regions of nonperfusion during temporary selective clamping [13]. CEUS has also been utilized for intraoperative guidance during radiofrequency ablation in addition to monitoring for treatment response and/or tumor recurrence in the perioperative period [16, 17].

CEUS has several unique characteristics that lend itself to intraoperative use. Unlike standard grey-scale US, CEUS provides exceptional visualization of tumor microvasculature not possible with color Doppler and allows for real-time assessment of tumor enhancement/washout due to the contrast agent's short half-life [4, 9, 18]. In our series, the ability to clearly identify the enhancing tumor microvasculature aided in tumor visualization and preservation of the majority of healthy parenchyma during resection. Finally, given that there is no ionizing radiation or risk of nephrotoxicity with CEUS, the study can be repeated with multiple injections of contrast if

needed.

Despite its advantages, CEUS also has potential limitations. As for all forms of sonography, CEUS image quality is user and equipment dependent. Additionally, the microbubble contrast agent increases cost when compared to conventional US but is more cost-effective than cross-sectional imaging with MRI. As demonstrated in patient 4 in our series, CEUS may not be as beneficial following TKI therapy due to reduced tumor vascularity. Finally given many urologists' lack of experience with this modality, CEUS requires intraoperative assistance from a radiologist, at least early in the experience.

5. Conclusion

CEUS has favorable diagnostic features including its safety in patients with CKD, lack of ionizing radiation, excellent visualization of tumor microvasculature and assessment of enhancement, and ease of use. While conventional US is usually sufficient for intraoperative tumor visualization, CEUS can be considered during PN for more complex endophytic, infiltrative or hilar tumors where accurate delineation of tumor contour is critical. CEUS is safe and may facilitate optimal nephron-mass preservation during tumor excision/reconstruction. Further experience with this modality will be required to define its ultimate utility during PN. Future directions for research may include a prospective study comparing intraoperative use of CEUS to conventional ultrasound to assess the efficiency, utility, and cost-effectiveness of intraoperative CEUS in partial nephrectomy. Furthermore, a larger sample may elucidate clinical scenarios that were not cited in this series where CEUS may be favored over conventional ultrasound.

Author Contribution

All authors have read and approved the final version of the manuscript before submission.

Conflict of Interest Statement

The authors declare they have no competing interests.

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