

Contrast enhanced ultrasound in urothelial carcinoma of urinary bladder: An underutilized staging and grading modality

Vijayant Govinda Gupta¹, Santosh Kumar², Shrawan Kumar Singh¹, Anupam Lal³, Nandita Kakkar⁴

¹Post Graduate Institute of Medical Education and Research, Chandigarh, India

²Department of Urology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

³Department of Radiodiagnosis, Post Graduate Institute of Medical Education and Research, Chandigarh, India

⁴Department of Histopathology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Citation: Gupta VG, Kumar S, Singh SK, Lal A, Kakkar N. Contrast Enhanced Ultrasound in urothelial carcinoma of urinary bladder: An underutilized staging and grading modality. Cent European J Urol. 2016; 69: 360-365.

Article history

Submitted: July 18, 2016

Accepted: Oct. 11, 2016

Published online: Nov. 30, 2016

Corresponding author

Santosh Kumar

Post Graduate Institute of Medical Education and Research

Department of Urology
160012 Chandigarh, India
phone: +91 941 737 4067
santoshp1967jaimatadi@yahoo.co.in

Introduction To evaluate contrast enhanced ultrasound (CEUS) as a modality to predict T stage of cancer of urinary bladder (CAUB) and to predict the grade of the tumor preoperatively.

Material and methods 110 patients with CAUB presenting to the Department of Urology at our institution between July 2014 and December 2015 underwent CEUS prior to endoscopic resection and the CEUS findings were compared with histopathology results.

Results CEUS had a sensitivity of 75, 65 and 90% and specificity of 95, 85 and 92% in detecting Ta, T1 and muscle invasion respectively. CEUS had a sensitivity of 78% and specificity of 85% in detecting the grade of the lesion.

Conclusions CEUS is a good alternative for T staging and grading of CAUB preoperatively. It is uniquely advantageous in detecting clots or necrosis and in patients with low eGFR where other imaging modalities are contraindicated.

Key Words: bladder cancer ◊ contrast enhanced ultrasound ◊ staging
◊ grading ◊ urology ◊ urooncology

INTRODUCTION

Urothelial carcinoma (UC) is the most common variant of carcinoma of the urinary bladder (CAUB) [1]. It constitutes 98% of all cancer of urinary bladder [1]. CAUB most commonly presents with gross painless hematuria. The management of CAUB is different for different stages and grades of the disease. Patients with non-muscle invasive bladder cancer (NMIBC) are managed with endoscopic resection and surveillance whereas patients with muscle invasive disease (MIBC) need radical extirpative surgery. The grade of the disease has been found to cor-

relate with stage and is one of the primary drivers of the disease pathology. Thus, accurate staging and grading of UC is essential [2].

Conventional grey scale ultrasonography (USG) is a widely available, non-invasive examination and because of its low cost, it is often the first examination performed for patients presenting with hematuria, but it has limited utility in defining the disease. Contrast enhanced computed tomography (CECT) is the recommended investigation for staging of CAUB. However, its limitations include radiation exposure and contrast reactions. All patients will undergo cystoscopy and transurethral resection

of bladder tumor (TURBT) for histopathological confirmation. TURBT can miss lesions or inadequate resection may be performed. One study reported that a repeat procedure within 6 weeks of the first TURBT found residual disease in 30% of patients [3].

Contrast enhanced ultrasound (CEUS) is a recent advancement in ultrasound technology. It utilizes ultrasonographic contrast agents (UCA), which are microbubbles composed of a lipid shell containing inert gases. These bubbles distribute in the body along vascular channels and their presence is detected by USG based on the reverberations they produce when they come in contact with sound waves. The uptake of UCA can be used to stage and grade CAUB in real time [4]. In the present study we evaluate CEUS as a method to predict invasive UC and determine the grade of CAUB.

MATERIAL AND METHODS

The study was conducted in the Departments of Urology, Radiology and Histopathology at our institute from July 2014 to December 2015. The study was approved by independent internal and an external ethics committees. A total of 278 consecutive patients of either sex presenting to the Department of Urology at our institute with suspected CAUB who met the inclusion and exclusion criteria (Table 1) were screened for CEUS.

Inclusion criteria

1. All patients with suspected carcinoma of the urinary bladder were included in the study.

Exclusion criteria

1. Pregnancy
2. Patients with prior lower abdominal surgery
3. Patients who had undergone TURBT, TURP, any prior bladder surgery or have received intravesical chemotherapy or immunotherapy
4. Patients with recent myocardial infarction, angina pectoris, cardiac insufficiency, severe cardiac arrhythmia or a right-left cardiac shunt
5. Patients with severe pulmonary hypertension, uncontrolled systemic hypertension, acute respiratory distress syndrome or COPD
6. Patients with a history of severe contrast allergy or any known drug allergy
7. Morbidly obese patients (BMI >40)

All patients provided written informed consent. CEUS was performed a day prior to cystoscopy and TURBT by a single radiologist with more than

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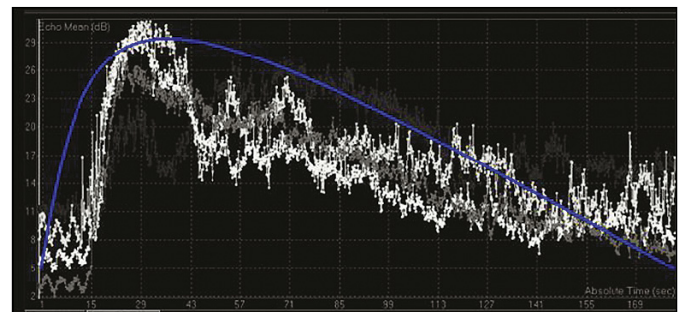


Figure 1. Type A contrast enhancement curve (db – decibel, sec – second).

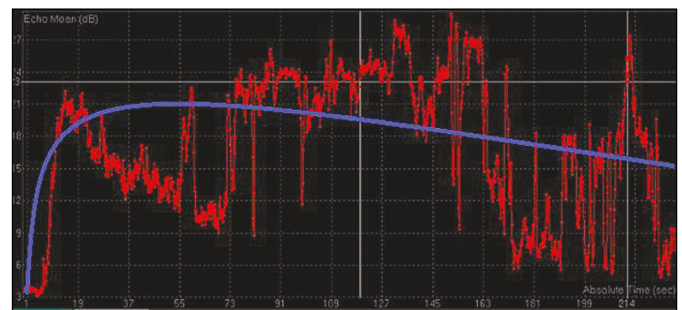


Figure 2. Type B contrast enhancement curve (db – decibel, sec – second).

10 years of experience in radiological evaluation of bladder cancer. CECT findings (if available) were not revealed to the operator. The same Philips IU 22 ultrasound with real time gray-scale and contrast harmonics was used to perform CEUS in all cases. A C5-1 pulse wave transducer with a frequency of 7.5 Hz and low mechanical index (0.047–0.115) was used. The patient was prepared for CEUS by confirming adequate bladder filling. Adequate bladder filling was confirmed by measuring the intravesical volume (250 to 300 ml) and ensuring

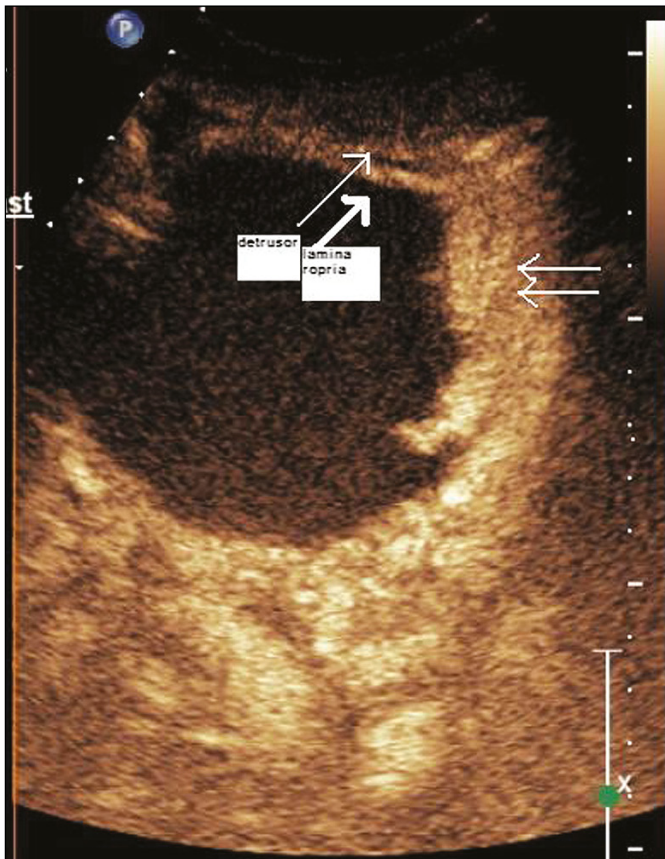


Figure 3. Contrast enhanced ultrasound image of a T2 lesion (TNM Tumor stage T2, double thin arrow showing site of invasion).

that the bladder wall was not thinned out. Initially, a B mode grey scale ultrasound was done to identify all lesions and to survey the bladder for mobile clots, any diverticula, large median lobe or vesical calculi. All visualized lesions were recorded. The lesion of interest was focused and gain increased and the harmonic imaging mode was entered. With the probe held constant, the patient was asked to respire in a controlled manner to reduce respiratory artifacts.

Intravenous reconstituted contrast (SonoVue) was injected as a bolus. The timer was started from the time of flush and the contrast phase was recorded for 3 minutes post injection. After the procedure was done, the patient was allowed to void and observed for 24 hours for any adverse effects. SonoVue (Bracco, Italy), is a powder which is reconstituted in the solvent for injection. The active substance in SonoVue is sulphur hexafluoride in the form of microbubbles. Each vial contains 59 mg sulphur hexafluoride. The vial is reconstituted with 5 ml of normal saline and after vibration blending; 2.4 ml (5 mg/ml) was used for injection.

After the procedure, each recording was analyzed on the same day using a propriety software from Philips called Q Labs which came preinstalled on the machine. The region of interest (ROI) was marked as a polygon on the lesion to be studied. The computer software automatically generated contrast enhancement curves. Two types of curve shapes emerged. In curve type A there was rapid enhancement with high peak enhancement and disappearance of contrast within 3 minutes (Figure 1). For the the second curve, type B, there was an early enhancement peak but slow plateau and contrast disappearance did not take place until the end of study (Figure 2). Based on a review of literature, type A curves corresponded to high-grade lesions and type B as low-grade [4].

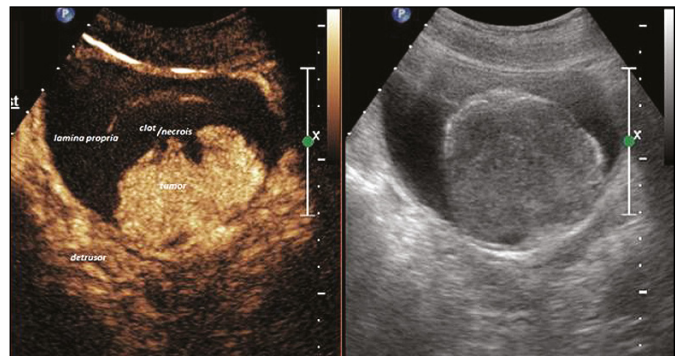


Figure 4. Composite image of contrast enhanced ultrasound and grey scale image of a T1 lesion (TNM tumor stage T1).

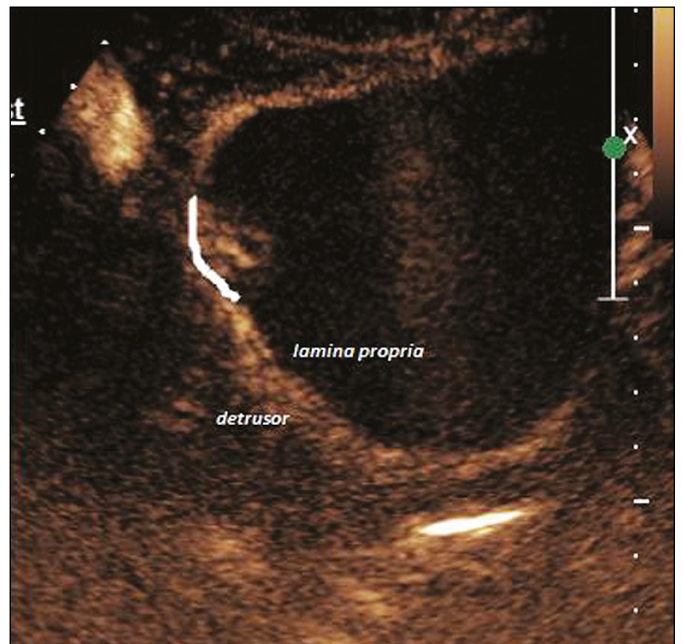


Figure 5. Contrast enhanced ultrasound image of a Ta lesion (TNM Tumor stage Ta).

On contrast injection, the bladder wall separated into two distinct enhancing layers corresponding to the lamina propria and the muscularis propria. Depending on visual inspection and operator experience, the lesions were classified as muscle invasive if there was loss of planes between the lesion and the muscularis propria (Figure 3). If there was no muscle invasion, then the lesion was classified as NMIBC. It was further subdivided into Ta and T1 based on invasion of lamina propria (Figures 4 and 5). All patients underwent TURBT at the Department of Urology by a surgeon with at least 5 years of experience. The specimen was processed at the Department of Histopathology. If the HPR revealed absence of deep muscle in the specimen, a repeat TURBT was performed. All histopathology specimens were reevaluated individually by a single pathologist with 10 years experience, who was blinded to the CEUS and cystoscopy findings.

Statistical methods and data analysis

Statistical analyses were performed using a computer software package (SPSS Inc. Chicago, IL). Student T tests and the Chi Square test were applied. For CEUS the sensitivity and specificity was calculated using histopathology as a gold standard.

RESULTS

Two hundred and seventy-eight (278) patients were found eligible for participation in the study. One hundred and eight patients did not give their consent. Forty-six patients could not undergo CEUS before TURBT. One hundred and twenty-four patients were enrolled in the study and underwent CEUS. Nine patients did not undergo restage TURBT after CEUS and were thus excluded. Three patients were excluded by the pathologist due to inability to determine grade and two patients had squamous cell variant of bladder cancer. In summary, for final analysis, 110 patients who had both CEUS and final histopathology were included for analysis.

The characteristics of the 110 patients and the final histopathology of the patients are shown in Table 2. The sensitivity, specificity and predictive value of CEUS in detecting T stage are shown in Table 3. CEUS can predict NMIBC and MIBC with a sensitivity of 90 and 90.74% respectively and specificity of 75.71 and 92.76% respectively. CEUS can predict Ta and T1 cancer with a sensitivity of 75 and 65.62% respectively and a specificity of 93.33 and 85.9% respectively.

The sensitivity, specificity and predictive value of CEUS enhancement curve in predicting the grade

Table 2. Characteristics of 110 patients

Parameter	Variable
Age	19–85 (median 60)
Sex	Male: 96 Female: 14
Hematuria	Yes: 102 No: 8
Histopathological T Stage	Ta: 21 T1:32 MIBC 53 Clot: 4
Histopathological Grade	Low grade: 36 High Grade: 70
CEUS Grade	Ta:21 T1:31 MIBC: 54 Clot: 4
CEUS Grade	Low Grade: 32 High Grade: 74

CEUS – Contrast enhanced ultrasound; T – tumor; NMIBC – non muscle invasive bladder cancer; MIBC – muscle invasive bladder cancer
The Ta lesions detected in CEUS are not the same as defined by pathology

Table 3. Diagnostic parameters of CEUS for T stage

T stage	Sensitivity	Specificity	PPV	NPV
Ta	75	93.33	71.43	94.38
T1	65.62	85.9	65.62	85.9
NMIBC (T1 +Ta)	90	75.71	67.92	92.98
MIBC	90.74	92.76	92.45	91.23

*NMIBC – non muscle invasive bladder cancer; MIBC – muscle invasive bladder cancer; PPV – positive predictive value; NPV – negative predictive value

Table 4. Type of enhancement curve in predicting grade

Grade	Sensitivity	Specificity	PPV	NPV
Low	78.12	85.14	69.44	90
High	85.14	78.12	90	69.44

PPV – positive predictive value; NPV – negative predictive value

are shown in Table 4. CEUS predicted low grade CAUB with a sensitivity, specificity, positive predictive value and negative predictive value of 78.12, 85.14, 69.44 and 90% respectively. CEUS predicted high grade CAUB with a sensitivity, specificity, positive predictive value and negative predictive value of 85.14, 78.12, 90 and 69.44% respectively.

DISCUSSION

Urothelial carcinoma of the urinary bladder is a common malignant neoplasm among smokers, with a rising incidence in India [2].

Macroscopic hematuria is an indication for complete evaluation of the genitourinary system for malignancy. Active hematuria can interfere with certain screening and diagnostic tests, such as malignant cytology. In our study, 4 patients were found to have organized clots in the bladder. The presence of clots in the bladder can hamper adequate evaluation of the bladder with CEUS. CEUS has a practical

advantage in this scenario as it can detect tumor vascularity and clot mobility in real time. A unique practical advantage of CEUS in evaluation of bladder tumor is that large papillary tumors with necrosis or adherent clots can be identified preoperatively and may help the surgeon in planning the resection. Patients with active hematuria on bladder irrigation pose a problem for CEUS, as stopping the irrigation can lead to clot formation and blockage of the return, causing the patient discomfort. Additionally, in situ large foley bulbs can hide small sessile lesions.

Serum creatinine may be raised in bladder cancer secondary to obstructive uropathy or due to CKD due to diabetes and hypertension. Serum creatinine has an effect on the choice of urinary diversion after cystectomy. Raised serum creatinine is a relative contraindication for CECT and MRI as it predisposes to nephropathy and nephrogenic systemic fibrosis respectively. CEUS has a significant advantage in this patient subgroup. UCA are metabolized and excreted by the lungs. In our study, 11 patients presented with a serum creatinine above 1.5 and all underwent CEUS without any toxicity or side effect.

In our study, pathology of TURBT specimens was used as the reference standard. This is a potential weakness of our study. Endoscopic resection was performed by different surgeons in the department depending on the OR schedule. TURBT can understage and overstage the disease. A study in 2014 showed that radical cystectomy post TURBT can change the T stage in more than half of the cases. All TURBT specimens were evaluated by the same pathologist with more than 10 years of experience in evaluating uro-oncology specimens. However, there can be significant inter reader variability among different pathologists. Tritschler et al. reported that just the knowledge of endoscopic findings could change the pathologist's interpretation. Studies have shown that there is significant inter observer variability and poor reproducibility in interpreting the grades of bladder cancer. Even with these drawbacks, our unique situation as a center in a resource poor setting prevented the use of a better methodology. Histopathology from radical cystectomy is ideal. The waiting period at our center can be long due to very high volumes and limited resources. Disease may progress during this period. Secondly, many patients received neoadjuvant chemotherapy prior to radical cystectomy. This demonstrates the variability in management of CAUB. Several factors including the resource setting can potentially modify the final treatment plan that the patient receives [5–8].

CEUS was able to delineate the T stage with specificity (85–100%) and sensitivity (75–92%) for tumor staging. CEUS was not able to accurately determine

lamina propria invasion. If Ta and T1 lesions were combined as NMIBC, then the sensitivity of the test improved but specificity declined. Our results are in concordance with previously published studies [9, 10, 11].

Differentiating lamina propria on CEUS is difficult. This wispy thin layer usually disappears with bladder overdistension. It is difficult to visualize in females and patients with thin bladders. Only in small solitary pedunculated tumors, can a comment on lamina propria be attempted. Differentiating Ta and T1 lesions is important for management decisions, as solitary Ta lesions require lesser follow up. However, from the surgeon's point of view, where most small solitary tumors will undergo en bloc resection with underlying muscle biopsy, the knowledge of Ta preoperatively does not make a difference in the surgical approach [7].

CEUS is truly unique in its ability to define the tumor grade preoperatively. We defined two types of TIC. When the type of curve was used to define the grade, we found that type A curve can define high-grade lesions with a sensitivity and specificity of 85 and 78% respectively ($p < 0.05$). Similarly, a type B curve correlates well with a low-grade lesion. This is similar to results reported previously in literature. Drudi et al. reported a sensitivity and specificity of 90 and 85% respectively [4]. Their higher accuracy may be due to consensus analysis by two radiologists and availability of supplementary information in the form of color Doppler.

The software that is used for the quantitative analysis a CEUS recording is different with different manufacturers [10, 11]. There are many types of propriety software available. The TIC values recorded will vary with the machine, probe, signal gain settings and the software being used [10, 11]. We also noticed that the amount of contrast used and the dilution used also had an effect on the TIC values. Thus, we feel that each center should develop their own TIC curves and cutoffs during preliminary examinations using these parameters as a rough guide until more robust data is available and there is homogeneous reporting of these values.

CONCLUSIONS

CEUS is a reliable investigation modality for preoperative characterization of urothelial carcinoma. It is an easily available, safe and non-invasive examination that is advantageous in patients with low GFR as it is not nephrotoxic.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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