Effectiveness of contrast-enhanced ultrasound for detecting the staging and grading of bladder cancer: a systematic review and meta-analysis

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Abstract

Aim: The study retrospectively analysed the accuracy of preoperative contrast-enhanced ultrasound (CEUS) in differentiating stage Ta-T1 or low-grade bladder cancer (BC) from stage T2 or high-grade bladder cancer. Material and methods: We systematically searched the literature indexed in PubMed, Embase, and the Cochrane Library for original diagnostic articles of bladder cancer. The diagnostic accuracy of CEUS was compared with cystoscopy and/or transurethral resection of bladder tumors (TURBT). The bivariate logistic regression model was used for data pooling, couple forest plot, diagnostic odds ratio (DOR) and summary receiver operating characteristic (SROC). Results: Five studies met the selection criteria; the overall number of reported bladder cancers patients were 436. The pooled-sensitivity (P-SEN), pooled-specificity (P-SPE), pooled-positive likelihood ratio (PLR+), pooled-negative likelihood ratio (PLR−), DOR, and area under the SROC curve were 94.0% (95%CI: 85%–98%), 90% (95%CI: 83%–95%), 9.5 (95%CI: 5.1–17.6), 0.06 (95%CI: 0.02–0.17), 147 (95%CI: 35–612) and 97% (95% CI: 95%–98%) respectively. Conclusion: CEUS reaches a high efficiency in discriminating Ta-T1 or low-grade bladder cancer from stage T2 or high-grade bladder cancer. It can be a promising method in patients to distinguish T staging and grading of bladder cancer because of its high sensitivity, specificity and diagnostic accuracy.

Keywords: urinary bladder neoplasms; bladder cancer; contrast-enhanced ultrasound; meta-analysis

Introduction

Bladder cancer (BC) ranks 10th in all new cases and deaths from cancer worldwide, which affects both women and man, reaching up to the 6th most common cancer diagnosed in men [1]. Most BC are urothelial carcinoma and approximately 75% of BC are non-muscle-invasive bladder cancers (NMIBC) [2]. The tumor is confined to the mucosa or invasion up to the lamina propria or carcinoma in situ (CIS), whereas the tumor invasion into the muscularis propria are defined as muscle-invasive bladder cancer (MIBC) [3]. In histopathological staging, high-grade BC (WHO grade II and III) and low-grade BC (WHO grade I) have significant differences in the prognosis of tumor patients [4]. The major treatment of NMIBC (Ta-T1) or low-grade BC is the complete resection of the tumor followed by the use of intravesical adjuvant. Radical cystectomy followed by neoadjuvant chemotherapy is the current standard treatment for MIBC (T2) or high-grade BC [5]. Thus, early detection and accurate staging and grading diagnosis are very critical for individual patients for optimizing treatment strategies.

Definitive diagnostic of BC relies on cystoscopy and transurethral resection of bladder tumors (TURBT), but
cystoscopy is highly invasive, expensive and requires anesthesia procedure, which can cause urinary tract infection and hematuria [6]. In BC, TURBT remains a reliable method of establishing stages and grades by removing all visible pathology [7], but has several limitations. When specimens are fragmented, unoriented and highly cauterized samples, pathologists have difficulty identifying whether the tumors invasion of the lamina propria or muscularis propria, which has close correlation to the options of treatment [8,9].

Conventional ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive examinations but with variable accuracy. Contrast-enhanced CT can effectively determine the stage of BC but it has exposure of radiation and contrast reactions [10].

Contrast-enhanced US (CEUS) is used to assess the tissue vascularization and neoplasms perfusion [11]. The technique can distinguish the clots and necrosis effectively by the contrast agent microbubbles perfusion in the mass. The advantage of CEUS is the non-nephrotoxicity, especially in patients with low glomerular filtration rate (GFR). CEUS can not only observe the perfusion of BC in real-time, but also has a unique imaging feature in identifying the various layers of the bladder wall; the bladder muscle layer shows slow and low enhancement, while the mucosal layer, particularly in the submucosa layer, showed rapid and sustained high enhancement [12].

The aim of this study was to assess the value of CEUS in BC detection of differentiating stage Ta-T1 or low-grade BC from stage T2 or high-grade BC, as imaging methods effectively to predict the T stage and the grade diagnostic potential of the tumor preoperatively.

Material and methods

Search strategy

PubMed, EMBASE and the Cochrane Library were used to search the literature up to July 14, 2020. The following keywords were used: (contrast-enhanced ultrasonography OR CEUS OR contrast-enhanced ultrasound OR CE ultrasound OR contrast-enhanced sonography) AND (Urinary Bladder Neoplasms OR Carcinoma, Transitional Cell OR transitional cell carcinoma OR bladder cancer* OR bladder carcinoma* OR bladder maligna* OR carcino* of bladder OR bladder neoplas* OR bladder metasta* OR bladder mass* OR TCC OR transitional cell OR urothelial carcinoma*). The literature search was performed without language restrictions. Only studies evaluating the diagnostic accuracy of BC by CEUS were included and the references were searched to ensure that all required studies were found.

The cystoscopy and/or TURBT was used as the reference standard; the results were estimated by the pooled sensitivity (P-SEN), specificity (P-SPE), pooled positive likelihood ratio (PLR+), negative likelihood ratio (PLR-), and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CI), area under the summary receiver operating characteristic (SROC).

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) CEUS is used for preoperative diagnosis local staging in patients with unknown or suspected BC patients; 2) included biopsy-proven based on cystoscopy and/or TURBT results; and 3) the published data permit to include the result in 2×2 tables for assessment of the diagnostic performance of CEUS for differentiating Ta-T1 or low-grade BC from T2 or high-grade BC.

Exclusion criteria were as followed: 1) relevant articles with low methodological quality; 2) without original data for 2×2 tables analysis; 3) studies of CEUS in the diagnostic of BC, but not to distinguish between Ta-T1 or low-grade BC and T2 or high-grade BC; 4) patients overlapping; and 5) studies sample size less than 30 individuals.

Data extraction and quality assessment

Two researchers (S.Y. Z and J. C.) independently extracted the information of the included studies: 1) study data: first author, publication year and country of origin; 2) demographic characteristics: Mean age (years) and sex; 3) reference standard; 4) preoperative CEUS classification: TP (True positive rate): MIBC at histology or high-grade BC (CEUS+); TN (True negative rate): NMIBC or low-grade BC (CEUS-); FP (False positive rate): NMIBC at histology or low-grade BC (CEUS+); FN (False negative rate): MIBC at histology or high-grade BC (CEUS-); sensitivity and specificity.

Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [13] tool was used independently by two reviewers with no disagreements.

Statistical analysis

All analyses were performed by using Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) and Stata 14.0 (Stata Corp, College Station, TX, USA). We extracted the data from the eligible literature and formed a four-fold table. PLR+ was defined as the likelihood that CEUS result positively for differentiating T2 or high-grade BC from Ta-T1 or low-grade BC would occur in patients with T2 or high-grade BC. PLR- was defined as the likelihood that CEUS result negative for differentiating T2 or high-grade BC from Ta-T1 or low-grade BC would occur
in patients without T2 or high-grade BC. The bivariate random effect model is preferred in the study of diagnostic accuracy when heterogeneity exists [14-17]. The Stata 14.0 was used to draw forest plots of a P-SEN and P-SPE, diagnostic score and DOR along with 95% confidence intervals (CI), and SROC curve were used to examine the diagnostic accuracy. F-statistic and Cochrane statistic p-value were used to assess the interstudy heterogeneity, if the $I^2 < 0.5$ or Cochran Q statistic p $> 0.1$, no heterogeneity was found; if the $I^2 > 0.5$ or Cochran Q statistic p $< 0.1$ a random-effects model was selected to indicated the heterogeneity’s result [18].

Deek’s funnel plot was the best method to detect publication bias, if no publication bias exists, the data obtained from each study will be distributed in an inverted funnel shape. Otherwise, the asymmetric inverted funnel graph indicates the existence of sample bias in the study [19].

**Results**

**Literature searches**
Our database search identified 274 papers from which 40 records were removed due to duplication 215 were excluded after screening the titles and abstracts and 14 studies were excluded because the staging accuracy was not reported. Finally, five studies were included in meta-analysis [10,20-23]. No additional articles were found in references. In figure 1 the process of selection is detailed.

**Study characteristics**
The included articles were published by authors from China (n=2), Italy (n=2) and India (n=1), had a totally of 436 suspected BC patients with mean age ranging from 60 to 68 years. A total of 222 BC were classified as positive and 214 lesions were negative at CEUS; 78 proved to be MIBC at histology, 118 NMIBC [10,20,22], 144 high-grade BC and 96 low-grade BC [21,23]. Table I summarizes the main characteristics of the included study.

**Methodology quality assessment**
According to the methodological assessment from the QUADAS-2 checklist, all the studies were prospective design, indicated the included studies good quality, all the studies enrolled consecutive patients and the cystoscopy and/or TURBT as the reference standard. Case selection, trials to be evaluated, gold criteria and clinical applicability had a low risk, the results are detailed in figure 2.

**Data synthesis and analysis**
As shown in figure 3, the primary analysis revealed that the P-SEN (I2=62.02%, Q=10.53, p=0.03>0.01), P-SPE (I2=45.69%, Q=7.37, p=0.12>0.01), indicated no significant heterogeneity was found. The P-SEN, P-SPE and DOR were 94.0% (95%CI: 85%–98%), 90% (95%CI: 83%–95%) and 147.31 (95%CI:35.44–612.35) respectively, PLR+ was 9.5 (95%CI:5.13–17.6) and PLR− was 0.06 (95%CI: 0.02–0.17), PLR+ that is greater than 5 and an PLR− that is less than 0.2 provide “strong”

Table 1. Characteristics and diagnostic performance of included studies

| Author         | N  | Design   | Age (mean, years) | Male (%) | Reference Standards   | TP | FN | FP | TN | Sen | Spe |
|----------------|----|----------|-------------------|----------|-----------------------|----|----|----|----|-----|-----|
| Caruso, 2010 [20] | 34 | Prospective | 61               | 94.1     | Cystoscopy and TURBT   | 9  | 0  | 2  | 21 | 1   | 0.913 |
| Drudi, 2012 [21]  | 144| Prospective | 68               | 66.6     | Cystoscopy and TURBT   | 80 | 8  | 8  | 48 | 0.909 | 0.857 |
| Li, Q, 2012 [22]  | 60 | Prospective | 62               | 75       | Cystoscopy and TURBT   | 15 | 0  | 6  | 36 | 0.857 | 0.857 |
| Gupta, 2016 [10]  | 110| Prospective | 60               | 87.3     | Cystoscopy and TURBT   | 53 | 1  | 1  | 52 | 0.982 | 0.981 |
| Li, 2017 [23]     | 192| Prospective | 66.7             | NR       | TURBT                 | 48 | 8  | 6  | 34 | 0.857 | 0.850 |

TURBT: transurethral resection of bladder tumors; NR: not reported; TP: True positive rate; TN: True negative rate; FP: False positive rate; FN: False negative rate; Sen: Sensitivity; Spe: Specificity;
diagnostic evidence [24], the area under the SROC curve were 97% (95% CI: 95%–98%), which suggested high diagnostic accuracy. Fagan diagram was drawn according to Bayes principle, after the test, the PLR+ increased from 20% to 70%, while the PLR− decreased to 2% (fig 4-7).

Publication bias
The Deeks’ funnel plot was used to indicate a systematic error in publication bias. The p-value was 0.97 and the regression line’s both sides distributed the included studies, indicating no clear evidence of publication bias (fig 8).

Discussion
In the BC patients, the 10-year recurrence was found to be 74.3% [25], 50% of patients with stage T1 BC may be high-grade at the time of diagnosis, with a progression rate of 30-50% [26]. For this reason, the selection of early accurate diagnosis modalities and efficient treatment is very important for the prognosis of BC patients. Compared with cystoscopy/TURBT, the advantages of CEUS are related to the possibility of creating a full dataset of the examination and using images for retrospective re-evaluation. This will compensate the operator dependent differences and thus more objectively evaluate the diagnosis results of CEUS [27] for the Ta-T1 of BC patients who are not suitable for repeating cystoscopy. Also, CEUS can be used as a noninvasive examination...
method for postoperative follow-up and can provide effective imaging information. Unlike other previous studies [28-31], our study mainly analyzed the accuracy of CEUS in the diagnosis of BC invasion degree by taking histology as the reference standard.

We evaluated the diagnostic accuracy of CEUS for differentiating T2 or high-grade BC from Ta-T1 or low-grade BC and we found the P-SEN of 94.0% (95%CI: 85%–98%) and P-SPE of 90% (95%CI: 83%–95%), thus confirming the higher accuracy of CEUS in the staging and grading of BC. CEUS can achieve equivalent P-SEN and P-SPE compared with MR imaging in staging and grading of the BC [32-33], indicating that CEUS is truly a valuable imaging method for defining the tumor invasion preoperatively. LR are comprehensive indicators reflecting the diagnostic value of diagnostic experiments [34]. In our study, PLR+ was 9.5 (95%CI:5.13–17.6) and PLR− 0.06 (95%CI: 0.02–0.17), providing “strong” diagnostic evidence. The DOR was 147.31 (95%CI:35.44–612.35) and the area under the SROC curve of 97% (95% CI: 95–98). In terms of these findings, CEUS demonstrates a high diagnostic performance in the diagnosis of BC in both NMIBC and MIBC patients, the differentiation between MIBC and NMIBC being crucial, as they show different prognosis and generally are treated with different approaches.

CEUS could not accurately determine the lamina propria invasion; this wispy thin layer usually disappears with bladder overdistension and is especially difficult to visualize in female and patients with thin bladders. For this reason, we combined Ta and T1 lesions as NMIBC, which would lead to an increase in P-SEN and a decrease in P-SPE, the results being in concordance with previ-
souls published studies [10,20,21]. In Gupta et al study [10] where the patients were evaluated by CEUS to predict T stage and the grade of BC, the SEN of CEUS in the diagnosis of BC staging was higher than that of BC grading, suggesting that the diagnostic value of CEUS for staging of BC might be higher. In our meta-analysis, the low number of included studies did not allow for subgroup analyses, so further studies are needed to evaluate the diagnostic value of CEUS in comparing the stages of BC with the grades of BC.

In our study the P-SEN and PLR, with 95% CI forest plots displayed moderate heterogeneity; we have three explanations for this. First, this could be due to the operator’s CEUS interpretation, different groups of grading and staging study design and patients features. Secondly, CEUS may increase diagnostic sensitivity in patients with high suspicion of BC, even though the radiologists who conduct CEUS studies and review CEUS images did not know the results of cystoscopy and/or TURBT histology. Thirdly, a limited number of Ta-T1 or low-grade BC and stage T2 or high-grade BC were studied.

This is the first meta-analysis to explore the diagnostic accuracy of CEUS for detecting the staging and grading of BC. All the studies were prospectively designed guaranteeing the robustness of the result, CEUS appears to reach a good performance in predicting the T stage and the grade of the BC preoperatively.

Conclusion

In conclusion, our meta-analysis demonstrates that CEUS has a high efficiency in discriminating Ta-T1 or low-grade BC from stage T2 or high-grade BC, due to the high P-SEN, P-SPE and diagnostic accuracy. CEUS is a promising imaging technique for distinguishing T staging and grading of BC.

Conflicts of interest: none

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Tan WS, Kelly JD. Intravesical device-assisted therapies for non-muscle-invasive bladder cancer. Nat Rev Urol 2018;15:667-685.
3. Kamat AM, Hahn NM, Efstratiou JA, et al. Bladder cancer. Lancet 2016;388:2796-2810.
4. Montironi R, Lopez-Beltran A. The 2004 WHO classification of bladder tumors: a summary and commentary. Int J Surg Pathol 2005;13:143-153.
5. Ge P, Wang L, Lu M, et al. Oncological Outcome of Primary and Secondary Muscle-Invasive Bladder Cancer: A Systematic Review and Meta-analysis. Sci Rep 2018;8:7543.
6. Hirotsu Y, Yokoyama H, Amemiya K, et al. Genomic profile of urine has high diagnostic sensitivity compared to cytology in non-invasive urothelial bladder cancer. Cancer Sci 2019;110:3235-3243.
7. Jimenez RE, Gheiler E, Oskanian P, et al. Grading the invasive component of urothelial carcinoma of the bladder and its relationship with progression-free survival. Am J Surg Pathol 2000;24:980-987.
8. Paner GP, Brown JG, Lapetino S, et al. Diagnostic use of antibody to smoothelin in the recognition of muscularis propria in transurethral resection of urinary bladder tumor (TURBT) specimens. Am J Surg Pathol 2010;34:792-799.
9. Miyamoto H, Sharma RB, Illei PB, Epstein JI. Pitfalls in the use of smoothelin to identify muscularis propria invasion by urothelial carcinoma. Am J Surg Pathol 2010;34:418-422.
10. 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.
11. Serafin Z, Bialecki M, Bialecka A, Sconfienza LM, Klopopka M. Contrast-enhanced Ultrasound for Detection of Crohn’s Disease Activity: Systematic Review and Meta-analysis. J Crohns Colitis 2016;10:354-362.
12. Scattoni V, Da Pozzo LF, Colombo R, et al. Dynamic gadolinium-enhanced magnetic resonance imaging in staging of superficial bladder cancer. J Urol 1996;155:1594-1599.
13. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529-536.
14. Suh CH, Park SH. Successful Publication of Systematic Review and Meta-Analysis of Studies Evaluating Diagnostic Test Accuracy. Korean J Radiol 2016;17:5-6.
15. Kim KW, Lee J, Choi SH, Huh, J, Park SH. Systematic Review and Meta-Analysis of Studies Evaluating Diagnostic Test Accuracy: A Practical Review for Clinical Researchers-Part I. General Guidance and Tips. Korean J Radiol 2015;16:1175-1187.
16. Lee J, Kim KW, Choi SH, Huh J, Park SH. Systematic Review and Meta-Analysis of Studies Evaluating Diagnostic Test Accuracy: A Practical Review for Clinical Researchers-Part II. Statistical Methods of Meta-Analysis. Korean J Radiol 2015;16:1188-1196.
17. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zw dollarsman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005;58:982-990.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj 2003;327:557-560.
19. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005;58:882-893.
20. Caruso G, Salvaggio G, Campisi A, et al. Bladder tumor staging: comparison of contrast-enhanced and gray-scale ultrasound. AJR Am J Roentgenol 2010;194:151-156.
21. Drudi FM, Di Leo N, Malpassini F, Antonini, F, Corongiu E, Iori F. CEUS in the differentiation between low and high-grade bladder carcinoma. J Ultrasound 2012;15: 247-251.
22. Li QY, Tang J, He EH, et al. Clinical utility of three-dimensional contrast-enhanced ultrasound in the differentiation between noninvasive and invasive neoplasms of urinary bladder. Eur J Radiol 2012;81:2936-2942.
23. Li Q, Tang J, He E, Li Y, Zhou Y, Wang B. Differentiation between high- and low-grade urothelial carcinomas using contrast enhanced ultrasound. Oncotarget 2017;8:70883-70889.
24. Halligan S, Altman DG. Evidence-based practice in radiology: steps 3 and 4--appraise and apply systematic reviews and meta-analyses. Radiology 2007;243:13-27.
25. Chamie K, Litwin MS, Bassett JC, et al. Recurrence of high-risk bladder cancer: a population-based analysis. Cancer 2013;119:3219-3227.
26. Pashos CL, Botteman MF, Laskin BL, Redaelli A. Bladder cancer: epidemiology diagnosis, and management. Cancer Pract 2002;10:311-322.
27. Jokisch F, Buchner A, Schulz GB, et al. Prospective evaluation of 4-D contrast-enhanced-ultrasound (CEUS) imaging in bladder tumors. Clin Hemorheol Microcirc 2020; 74:1-12.
28. Wu M, Li L, Wang J, et al. Contrast-enhanced US for characterization of focal liver lesions: a comprehensive meta-analysis. Eur Radiol 2018;28:2077-2088.
29. Zhang F, Li R, Li G, Jin L, Shi Q, Du L. Value of Contrast-Enhanced Ultrasound in the Diagnosis of Renal Cancer and in Comparison With Contrast-Enhanced Computed Tomography: A Meta-analysis. J Ultrasound Med 2019;38:903-914.
30. Li XZ, Song J, Sun ZX, Yang YY, Wang H. Diagnostic performance of contrast-enhanced ultrasound for pancreatic neoplasms: a systematic review and meta-analysis. Dig Liver Dis 2018;50:132-138.
31. Ma X, Zhao Y, Zhang B, et al. Contrast-enhanced ultrasound for differential diagnosis of malignant and benign ovarian tumors: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2015;46:277-283.
32. Huang L, Kong Q, Liu Z, Wang J, Kang Z, Zhu Y. The Diagnostic Value of MR Imaging in Differentiating T Staging of Bladder Cancer: A Meta-Analysis. Radiology 2018;286:502-511.
33. Gandhi N, Krishna S, Booth CM, et al. Diagnostic accuracy of magnetic resonance imaging for tumour staging of bladder cancer: systematic review and meta-analysis. BJU Int 2018;122:744-753.
34. Jaeschke R, Guyatt GH, Sackett DL. Users’ guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. JAMA 1994;271: 703-707.