REVIEW PAPER

UROLOGICAL ONCOLOGY

Contrast-enhanced ultrasound in the diagnosis of neoplastic lesions of the urinary bladder

Jakub Kufel[1], Adam Mitręga[2,3], Mikołaj Magiera[2], Michał Bielówka[2,3]

[1]Department of Radiodiagnostics, Interventional Radiology, and Nuclear Medicine, Medical University of Silesia, Katowice, Poland
[2]Students' Scientific Association of Computer Analysis and Artificial Intelligence at the Department of Radiology and Nuclear Medicine, Medical University of Silesia, Katowice, Poland
[3]Department of Biophysics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland

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Corresponding author
Adam Mitręga
Students' Scientific Association of Computer Analysis and Artificial Intelligence at the Department of Radiology and Nuclear Medicine,
Medical University of Silesia,
Katowice, Poland
adam.mitrega2306@gmail.com

Introduction Cystoscopy remains the gold standard of diagnosis and follow-up for bladder cancer (BC); however, it is an invasive procedure associated with discomfort and potential complications. Contrast-enhanced ultrasound (CEUS) emerges as an alternative, utilizing real-time assessment of tumor vascularization and perfusion. The aim of this systematic review was to evaluate its diagnostic performance for BC detection.

Material and methods MEDLINE (PubMed), Scopus, Web of Science Core Collection and Embase databases were queried through July, 2024. We included studies reporting on the diagnostic accuracy of CEUS for the detection of BC.

Results Out of 883 individual records, we identified 6 reports of prospective and retrospective studies, comprising 894 patients. The included studies indicate that CEUS demonstrates high diagnostic sensitivity, and specificity in discriminating malignant from benign bladder tumors. Moreover, CEUS has been shown promising performance in the preoperative prediction of tumor grade and stage, offering diagnostic capabilities comparable to well-established non-invasive imaging techniques.

Conclusions Our findings support the utilization of CEUS as adjunct to existing BC diagnostic protocols. It represents an alternative for BC diagnosis and could benefit patients contraindicated for conventional imaging modalities or at high-risk of cystoscopy-related complications. Scant amount of standardized, large-scale, prospective, comparative investigations are available, thus further research is necessary to validate the clinical utility of CEUS in BC detection.

Key Words: contrast-enhanced ultrasound ‹› bladder cancer ‹› non-invasive imaging

INTRODUCTION

The diagnosis and staging of bladder cancer primarily rely on cystoscopy. This method enables direct visualization and biopsy, and it is commonly used for primary diagnosis [1]. Despite being invasive, it also plays a key role in the transurethral resection of the tumor (TURBT) [2]. Contrast-enhanced computed tomography (CT) remains the primary imaging tool for assessing lymph node involvement and upper urinary tract anatomy. It is considered the gold standard for staging muscle-invasive bladder cancer (MIBC); however, it involves radiation exposure and carries a risk of adverse reactions to contrast agents [3]. Despite its broad use, CT cannot reliably determine muscle invasion, unlike magnetic resonance imaging (MRI). Recently, bladder MRI combined with the Vesical Imaging-Reporting and Data System (VI-RADS) has emerged as a promising method for local staging of bladder cancer, particularly for assessing muscle invasion [4]. That said, MRI remains a limited resource due to high costs and limited accessibility, which hinders its widespread implementation in routine clinical practice [5].

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Other imaging modalities, such as ultrasonography, are also utilized in the diagnostic workup of bladder cancer [3]. In recent years, contrast-enhanced ultrasonography (CEUS) has gained increasing attention for preoperative tumor staging in gastric, renal, and bladder cancers [3, 6, 7]. Intravenous administration of microbubble contrast agents enables detailed assessment of tissue vascularization and tumor perfusion [8, 9], as well as differentiation between clots or necrosis and viable tumor tissue [10].

The microbubble shell is composed of phospholipids, polymers, surfactants, or albumin, encapsulating gases such as perfluoropentane or sulfur hexafluoride, which are excreted via the lungs, thus bypassing renal metabolism [10]. This makes CEUS a safe imaging modality for patients with significant renal impairment, including those on dialysis [3].

Moreover, CEUS enables real-time assessment of tumor perfusion and allows for the differentiation of bladder wall layers. While the muscularis propria enhances slowly and weakly, the mucosal and especially submucosal layers show rapid and sustained enhancement [11].

Given the growing body of literature on the diagnostic accuracy of CEUS in detecting and staging bladder cancer, a systematic synthesis of available data is warranted. This study aims to evaluate the diagnostic performance of CEUS in the detection of neoplastic lesions of the urinary bladder.

MATERIAL AND METHODS

Search strategy and selection criteria

In July 2024, we conducted a systematic search in the MEDLINE (via PubMed), Scopus, Web of Science Core Collection, and Embase databases. The search strategy and research question was formulated with the aid of the PICO framework [12]. The detailed search strategy for each database is available in Supplement 1. Conflicts were resolved by a third, independent researcher. The agreement between researchers was assessed using Cohen's Kappa [13].

Inclusion and exclusion criteria and data extraction

We included retrospective and prospective studies, published within the last 10 years, reporting on the diagnostic performance of CEUS in detecting bladder neoplasms. We excluded case reports, case series, systematic reviews, meta-analyses, conference abstracts, studies assessing pediatric populations, or focusing on areas of the body other than the bladder, and studies only utilizing imaging techniques other than CEUS, such as CT or MRI.

Quality assessment

Studies were evaluated using the QUADAS-2 checklist [14]. For each included study, an item was rated negatively if it was not present in the article and positively if it was present. The results are presented in Suppl. Table 1.

Risk of bias assessment

All articles were assessed for risk of bias according to the Cochrane Handbook guidelines for non-randomized studies [15] by two independent reviewers based on the following domains: confounding, selections of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result (Suppl. Figure 1). All discrepancies were resolved by consensus.

RESULTS

A total of 2303 records were identified, of which six studies were deemed eligible, after title-abstract and full text selection (Suppl. Figure 2).

We identified two retrospective [16, 17] and three prospective (two non-comparative [18, 19] and one comparative [20]) studies, with one study including both prospectively and retrospectively collected data [21].

The most important characteristics of the included studies are presented in Table 1.

Data synthesis

Diagnostic performance attributes of CEUS are shown below (Table 2). All the statistical data shown below were compared with histopathologic findings after surgical removal of the lesion taken as a gold standard. In the study conducted by Guo et al. [16] and in the retrospective part of the study conducted by Li et al. [21] there was no comparison of CEUS performance with pathological diagnosis, due to the retrospective nature of the study.

Most of the authors divide detected lesions between LG (low-grade) and HG (high-grade) [16, 17, 19, 21], while Fu et al. [18] and Zhang et al. [17] extend the division to benign lesions. Liu et al. [20] only considered single and multiple lesions. This statistic was provided by only some of the authors [16, 17, 20, 21].

In the study conducted by Guo et al. [16], patients with pathologically confirmed bladder urothelial carcinoma (BUC) were examined using CEUS with TIC (time intensity curve) analysis (Table 3) to assess the value of this method in differentiating between LG and HG BUC, and to investigate the correlation with tumor microvessel density. The diagnosed lesions involved urothelial carcinoma of LG or HG, with a diameter exceeding 1 cm.

In the study conducted by Li et al. [21], the enhancement patterns of CEUS in bladder lesions were retrospectively analyzed and categorized between LG and HG lesions based on either fast or slow, wash-in and wash-out times. A subsequent prospective study was conducted in which CEUS was performed for the differential diagnosis of bladder lesions based on the criteria established in the prior study part. After statistical analysis, the value of CEUS in differentiating HG and LG urothelial carcinoma was evaluated. When the bladder contained multiple lesions, the researchers considered the largest untreated lesion of the bladder. High diagnostic performance was obtained in differentiating LG and HG lesions, where PPV, NPV, accuracy, sensitivity, and specificity values for both LG and HG lesions oscillated over 85% in each case, except NPV for HG lesions, achieving 82%. [21].

In the research carried out by Fu et al. [18], patients with bladder tumors larger than 5 mm in diameter were examined using CEUS and contrast-enhanced MRI. The study assessed the efficacy of both imaging modalities in differentiating benign from malignant lesions and, for malignant cases, in detecting muscle invasion or its absence. Histopathological analysis identified 120 cases of urothelial carcinoma of the bladder. Additionally, 36 benign lesions were identified. The comparative statistical analysis indicates that both CEUS and contrast-enhanced MRI exhibit similar diagnostic performance in differentiating between benign and malignant lesions, with overall accuracies of 85.90% and 84.62%, respectively. Contrast-enhanced MRI demonstrated a marginally higher sensitivity (95.00% vs 91.76%), whereas CEUS achieved superior specificity (66.67% vs 50.00%). In assessing muscularis invasion, CEUS yielded an accuracy, sensitivity, and specificity of 84.6%, 85.3%, and 83.3%, respectively. In comparison, MRI demonstrated slightly lower diagnostic metrics, with accuracy, sensitivity, and specificity of 76.9%, 79.4%, and 72.2%, respectively.

In the study by Gupta et al. [19], patients with suspected bladder urothelial carcinoma (BUC) underwent CEUS to preoperatively assess tumor stage and grade. The analysis included differentiation between MIBC and NMIBC, as well as subclassification into Ta and T1 based on lamina propria invasion. CEUS results were compared with histopathological findings following transurethral resection of bladder tumor (TURB). The method predicted NMIBC and MIBC with sensitivities of 90% and 90.5%, and specificities of 75.7% and 92.76%, respectively. For Ta and T1 staging, sensitivities were 75% and 65.6%, with specificities of 93.3% and 85.9%, respectively. Additionally, contrast-enhancement curves were generated during CEUS to classify BUC into low- and high-grade tumors, yielding satisfactory diagnostic performance (Tables 2, 3).

Zhang et al. included 173 bladder lesion cases to explore the application of CEUS for the diagnosis and grading of BUC. CEUS was used to observe the contrast agent perfusion condition and intensity of the focus. Then it compared the contrast agent perfusion intensity of the focus with that of the surrounding normal bladder wall. If it was stronger/lower than (or equal to) the normal bladder wall, it was "high enhancement/low enhancement", and if there was no contrast agent filling inside

Table 1. *Baseline characteristics*

Author	Number of patients	Mean age	Country	Study period	Male / Female	Ultrasound scanner	Contrast used	Lesions considered
Guo et al. [16]	105	63; 66*	China	2009–2016	29/76	Philips IU22 system	2.4 ml Sonovue	Low- and high-grade lesions; diameter >1 cm
Li et al. [21]	96 + 96**	(70; 63* + 64; 69*)**	China	2010–2015	80/16	Philips IU22 system	1.2 ml SonoVue	Largest, untreated lesion
Fu et al [18]	156	53	China	2021–2022	104/52	PHILIPS EPIQ 5	1.0 ml SonoVue	Newly diagnosed bladder neoplasms; diameter >5 mm
Gupta et al. [19]	110	–	India	2014–2015	96/14	Philips IU 22 system	2.4 ml Sonovue	Untreated, suspected bladder carcinoma lesions
Zhang et al. [17]	173	60	China	2019–2022	141/32	Philips Epiq 7	1.2 ml SonoVue	Carcinoma of urinary bladder
Liu et al. [20]	38	63	China	2013–2020	34/4	Aplio 500, Aplio i900	SonoVue	Bladder occupied lesions

TIC – time intensity curve
* Data separated by semicolon concerning first low- then high-grade changes
** Data separated by plus sign concerning first retro- then prospective study

the focus, it was "no enhancement". There were statistically significant differences between BUC and benign lesions in terms of color blood flow distribution intensity and CEUS enhancement intensity (both P < 0.05). The AUC, rising slope, and peak intensity of BUC were significantly higher than those of benign lesions (all P < 0.05). The H/T (height H / basal width T) value of 0.63 was the critical value for distinguishing HG and LG BUC, with a diagnostic sensitivity of 80.0% and a specificity of 60.0% [17].

In the study by Liu et al., 38 patients with bladder lesions identified on conventional ultrasound underwent both color Doppler flow imaging (CDFI) and CEUS. The study compared the ability of both techniques to visualize lesion vascularity and assessed CEUS perfusion patterns. Among 51 lesions, 6 were glandular cystitis, 2 inverted papillomas, and 43 malignant tumors (including 41 urothelial carcinomas, one colorectal, and one prostate metastasis). CEUS demonstrated a 100% blood flow detection rate, significantly higher than CDFI (62.7%, p <0.05). Based on perfusion characteristics, CEUS identified 46 malignant and 5 benign lesions, yielding a diagnostic accuracy of 86.3% [20].

Some of the authors [16, 17, 21] chose to analyze specific parameters of the flow of the contrast medium and time intensity curve (TIC). The data describing contrast flow given in Table 3 depict the information about the dynamics of contrast media assessing quantitative values of tumor vascularization.

Most of the statistics given in the individual articles have not been included in every work. Thus, it is not straightforward to compare the results because of the lack of concurring data. However, the results may allow us to determine between benign and malignant lesions. Results presented by Zhang et al. [17] as well as Li et al. [21] depict that the LG and HG lesions could potentially be differentiated by comparison of the parameters of contrast flow through the lesion vessels. Li et al. [21] suggested that the wash-out times and peak intensity are higher for the HG lesions compared to the LG group. Zhang et al. [17] showed that the blood flow distribution intensity was higher in the HG group compared to LG and benign lesions. Guo et al. [16] pointed out that their results showed no significant difference between LG and HG lesion vessel blood flow, except that TPH (time from peak to one-half the signal intensity) was higher in HG than in LG lesions and the semi-DS (semi-descending slope) was lower in the LG group compared to the HG group. The AUC for both TPH and semi-DS was determined at 0.79.

Table 2. *Statistical illustration of CEUS performance in predicting bladder neoplasms*

Author	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Li et al. [21]	85; 92	89; 82	88; 88	85; 86	89; 90
Fu et al. [18]*	–	–	86; 85	92; 85	67; 83
Gupta et al. [19]	70; 90	90; 70	–	78; 85	85; 78
Zhang et al. [17]	94	63	93	98	33
Liu et al. [20]	–	–	86	–	–

The values separated by semicolon predicting first low- then high-grade tumors
* The values separated by semicolon refer first to the performance in differentiating between benign and malignant lesions, and then to the prediction of bladder muscle invasion

Table 3. *Characterization of contrast flow in the included studies*

Contrast flow parameter	Guo et al. [16]	Li et al. [21]	Zhang et al. [17]
Arrival time for BC (s)	–	21.44 ±1.34; 22.13 ±1.76*	22.5±6.2
Arrival time for benign lesions (s)	–	–	23.4±6.4
Peak time for BC (s)	27.66 ±7.21; 28.24 ±4.33*	27.06 ±2.18; 29.31 ±2.14*	32.3 (27.0, 38.8)
Peak time for benign lesions (s)	–	–	31.5 (28.0, 34.9)
Peak intensity for BC	19.38 ±5.08; 17.76 ±5.57*	13.87 ±9.42; 19.85 ±12.13*	94.2 (36.5, 289.6)
Peak intensity for benign lesions	–	–	48.6 (16.8, 79.4)
AUC	0.79	–	0.72
Ascending slope for BC	–	–	12.5 (4.4, 40.0)
Ascending slope for benign lesions (s)	–	–	5.5 (2.2, 15.9)
Wash-out time (s)	–	20.18 ±8.27; 34.83 ±10.41*	–
Rise time (s)	8.40 ±3.31; 8.57 ±3.00*	–	–
Mean transit time (s)	32.44 ±12.63; 32.60 ±12.66*	–	–
Time to peak to one-half	41.72 ±9.78; 51.25 ±12.29*	–	–

* Values separated by plus sign concerning first low- then high-grade tumors

DISCUSSION

In this study, we analyzed the diagnostic accuracy of CEUS in detecting bladder cancer (BC). The results indicate consistently high accuracy, exceeding 85% across all included studies. However, individual diagnostic metrics such as PPV, NPV, sensitivity, and specificity varied, with some values as low as 63%, and specificity dropping to 33% in Zhang et al. [17]. These findings suggest that CEUS may be a promising tool for BC diagnosis. Its ability to visualize real-time tumor vascularization is particularly valuable. CEUS could aid in detecting malignant lesions, especially in patients with atypical symptoms or when conventional methods like cystoscopy are contraindicated or insufficient. Nevertheless, CEUS has several limitations. Its diagnostic performance may be reduced in cases of severe obesity due to signal attenuation, and image quality can be compromised by factors such as massive ascites or uterine prolapse. It is also less reliable for detecting tumors smaller than 5 mm and is suboptimal for assessing adjacent pelvic structures in T4-stage disease. Additionally, reduced acoustic penetration in large or heavily calcified tumors may impair lesion characterization. Furthermore, distinguishing benign lesions from low-grade bladder cancer remains challenging [18].

Cystoscopy is considered the gold standard for detection of HG BC because of its exceptionally high specificity (<2% false-positive rate). It is an invasive procedure, requiring anesthesia in some cases, and carries a risk of complications such as bleeding or infection [22]. Therefore, CEUS could emerge to be a safer, non-invasive alternative in certain clinical scenarios, particularly for patients with higher risk for complications. While CEUS may not replace cystoscopy in terms of direct visualization and biopsy capabilities, it can become a valuable addition by offering clinically important information about tumor perfusion and vascularization. A direct comparison of the effectiveness of cystoscopy and CEUS in detecting bladder lesions is challenging due to the limited availability of comprehensive studies on the subject. As of December 2024, there are two registered ongoing studies in that context [23, 24].

In cancer diagnostics, MRI is particularly valuable for tumor staging, which is essential for treatment planning. However, it is more costly and time-consuming compared to contrast-enhanced ultrasound (CEUS), which is cost-effective, widely accessible, and feasible in outpatient settings [21]. Notably, CEUS may offer certain advantages over MRI because it is easier to perform and does not significantly prolong the diagnostic workflow – an important consideration in the management of bladder cancer. Although CEUS may not match MRI in terms of staging precision, the study by Fu et al. [18] demonstrated comparable diagnostic accuracy between the two modalities in differentiating benign from malignant bladder lesions. Furthermore, CEUS slightly outperformed MRI in the assessment of muscular invasion, suggesting its potential as a practical and accessible tool for local staging and clinical decision-making. Nonetheless, the limited sample size in that study may restrict the generalizability of its findings [18].

CT is a widely available and utilized imaging technique in the diagnostic workup of hematuria and staging of muscle-invasive bladder cancer. It is particularly valuable for assessing tumor location, its size, and potential metastases. However, CT has certain limitations including the use of ionizing radiation, posing a risk for patients requiring frequent follow-up examinations [25]. Additionally, the contrast agents used in CT are nephrotoxic and therefore should be used with caution or not at all in patients with renal insufficiency. A precise comparison of the effectiveness of CT and CEUS in detecting bladder lesions is challenging due to the lack of comprehensive studies on the subject and non-standardized comparison methods.

In addition, CEUS with TIC analysis may in the future allow us, as Li et al. [21] and Zhang et al. [17] observed, to distinguish between LG and HG bladder lesions. The first aforementioned group of researchers observed that HG lesions are characterized by fast wash-in and slow wash-out enhancement pattern, while also exhibiting higher peak intensity and longer wash-out times compared to LG lesions, which show both fast wash-in and wash-out enhancement pattern. These parameters suggest greater vascular activity in more aggressive tumors. Zhang et al. [17] showed that the blood flow distribution is higher in the HG lesions compared to the LG ones. Guo et al. [16], on the other hand, presented no significant difference between blood flow information and tumor advancement, except for TPH positively linearly correlating with MVD and negatively linearly correlating with semi-DS. Tests showed an AUC of 0.79 for TPH and semi-DS, which is considered as a poor performance [26]. The method does not provide tumor staging, which is crucial for treatment planning [21]. For the time being, CEUS with TIC does not allow us to draw any meaningful conclusions.

While CEUS is not a new technology, recent studies indicate growing interest in its application for bladder cancer evaluation. For instance, a 2024 study conducted by Jing Han et al. introduced a CEUS-based VI-RADS scoring system to assess muscle invasion preoperatively [27]. However, it is worth noting that its broader clinical use remains limited, partly because it is not yet included in major urological guidelines.

Further research should focus on comparing the effectiveness of CEUS with cystoscopy and other advanced imaging methods, such as MRI and contrast-enhanced CT. Large-scale, multicenter, prospective studies involving larger patient populations are necessary to determine the long-term clinical benefits of CEUS in the diagnosis and monitoring of bladder cancer. Developing detailed standardization for the diagnosis of bladder cancer lesions using CEUS will help to maintain the high levels of sensitivity, accuracy, and specificity of this diagnostic method.

This systematic review has several limitations: first, the inclusion of only six studies, with each having various methodologies, limits the interpretation of the results. The bias may affect the comparability of outcomes, due to the differences within study designs, patient populations, and diagnostic criteria presented with non-concurring data. The retrospective nature of some studies [16, 17, 21] may lead to selection bias, which could lower the reliability of the findings. The operators' experience and variability in ultrasound equipment used across studies could influence the diagnostic accuracy and reproducibility of CEUS, which may further lead to outcome bias.

CONCLUSIONS

The results of this systematic review suggest that CEUS could potentially become an integral component of the diagnostic algorithm for bladder cancer in the future. After additional, standardized research, CEUS may offer a precise, rapid, and safe diagnostic method. Implementing CEUS into routine clinical practice in the future could enhance the quality of patient care by enabling easily accessible, accurate assessment and effective monitoring of bladder cancer lesions that could potentially save lives in the early stage of neoplasm.

CEUS also marks its potential use as a less invasive follow-up alternative to cystoscopy by highlighting tumor vascularity to help detect lesions and predict muscle invasion. For the time being, CEUS can complement other imaging techniques, such as CT or MRI, offering advantages such as the absence of radiation exposure and low nephrotoxicity.

To maximize the utility of CEUS in bladder cancer diagnostics, it is essential to conduct further studies across diverse populations and develop standardization for this method, ensuring greater reliability and accuracy of results, thereby increasing the likelihood of CEUS being widely implemented in clinical practice.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The ethical approval was not required.

SUPPLEMENTARY MATERIALS

Supplement 1. Search strategy (24.06.2024)

String:

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((PY=(2014-2024)) AND ALL=(contrast-enhanced ultrasonography OR contrast enhanced ultrasonography OR CE ultrasonography OR CEUS OR contrast-enhanced ultrasound OR contrast enhanced ultrasound OR CE ultrasound)) AND ALL=(OR Bladder Cancers OR Cancer Bladder OR Cancer of Bladder OR Cancer of the Bladder OR Malignant Tumor of Urinary Bladder OR Bladder Malignancy OR Bladder OR Urinary Bladder Carcinoma OR Carcinoma Transitional Cell OR Transitional Cell Carcinoma OR TCC in bladder OR urothelial carcinoma OR bladder metastases)

The search was conducted in two attempts, cause of the exceeding size of the string for ‘all fields' search

263+102 -> added Filters: Articles-> 214+85

214:
https://www.webofscience.com/wos/woscc/summary/ad8d114a-c704-4dad-b8c2-e3a55054ff93-f913a441/relevance/1
85:
https://www.webofscience.com/wos/woscc/summary/e47b4e88-3f6c-48ab-bb4f-cfe11838ac10-f913a837/relevance/1

Embase:
(‚neoplasm urinary bladder' OR ((‚neoplasm'/exp OR neoplasm) AND urinary AND (‚bladder'/exp OR bladder)) OR ‚urinary bladder neoplasm'/exp OR ‚urinary bladder neoplasm' OR (urinary AND (‚bladder'/exp OR bladder) AND (‚neoplasm'/exp OR neoplasm)) OR ‚bladder neoplasms'/exp OR ‚bladder neoplasms' OR ((‚bladder'/exp OR bladder) AND (‚neoplasms'/exp OR neoplasms)) OR ‚bladder neoplasm'/exp OR ‚bladder neoplasm' OR ((‚bladder'/exp OR bladder) AND (‚neoplasm'/exp OR neoplasm)) OR ‚neoplasm bladder'/exp OR ‚neoplasm bladder' OR ((‚neoplasm'/exp OR neoplasm) AND (‚bladder'/exp OR bladder)) OR ‚bladder tumors'/exp OR ‚bladder tumors' OR ((‚bladder'/exp OR bladder) AND (‚tumors'/exp OR tumors)) OR ‚bladder tumor'/exp OR ‚bladder tumor' OR ((‚bladder'/exp OR bladder) AND (‚tumor'/exp OR tumor)) OR ‚tumor bladder' OR ((‚tumor'/exp OR tumor) AND (‚bladder'/exp OR bladder)) OR ‚tumors bladder' OR ((‚tumors'/exp OR tumors) AND (‚bladder'/exp OR bladder)) OR ‚neoplasms, bladder' OR ((‚neoplasms,'/exp OR neoplasms,) AND (‚bladder'/exp OR bladder)) OR ‚urinary bladder cancer'/exp OR ‚urinary bladder cancer' OR (urinary AND (‚bladder'/exp OR bladder) AND (‚cancer'/exp OR cancer)) OR ‚cancer urinary bladder' OR ((‚cancer'/exp OR cancer) AND urinary AND (‚bladder'/exp OR bladder)) OR ‚bladder cancer'/exp OR ‚bladder cancer' OR ((‚bladder'/exp OR bladder) AND (‚cancer'/exp OR cancer)) OR ‚bladder cancers' OR ((‚bladder'/exp OR bladder) AND (‚cancers'/exp OR cancers)) OR ‚cancer bladder' OR ((‚cancer'/exp OR cancer) AND (‚bladder'/exp OR bladder)) OR ‚cancer of bladder' OR ((‚cancer'/exp OR cancer) AND of AND (‚bladder'/exp OR bladder)) OR ‚cancer of the bladder'/exp OR ‚cancer of the bladder' OR ((‚cancer'/exp OR cancer) AND of AND the AND (‚bladder'/exp OR bladder)) OR ‚malignant tumor of urinary bladder' OR (malignant AND (‚tumor'/exp OR tumor) AND of AND urinary AND (‚bladder'/exp OR bladder)) OR ‚bladder malignancy'/exp OR ‚bladder malignancy' OR ((‚bladder'/exp OR bladder) AND (‚malignancy'/exp OR malignancy)) OR ‚bladder'/exp OR bladder OR ‚urinary bladder carcinoma'/exp OR ‚urinary bladder carcinoma' OR (urinary AND (‚bladder'/exp OR bladder) AND (‚carcinoma'/exp OR carcinoma)) OR ‚carcinoma, transitional cell'/exp OR ‚carcinoma, transitional cell' OR ((‚carcinoma,'/exp OR carcinoma,) AND transitional AND (‚cell'/exp OR cell)) OR ‚transitional cell carcinoma'/exp OR ‚transitional cell carcinoma' OR (transitional AND (‚cell'/exp OR cell) AND (‚carcinoma'/exp OR carcinoma)) OR ‚tcc in bladder' OR (tcc AND in AND (‚bladder'/exp OR bladder)) OR ‚urothelial carcinoma'/exp OR ‚urothelial carcinoma' OR (urothelial AND (‚carcinoma'/

exp OR carcinoma)) OR ‚bladder metastases'/exp OR ‚bladder metastases' OR ((‚bladder'/exp OR bladder) AND (‚metastases'/exp OR metastases))) AND (‚contrast-enhanced ultrasonography'/exp OR ‚contrast-enhanced ultrasonography' OR (‚contrast enhanced' AND (‚ultrasonography'/exp OR ultrasonography)) OR ‚contrast enhanced ultrasonography'/exp OR ‚contrast enhanced ultrasonography' OR ((‚contrast'/exp OR contrast) AND enhanced AND (‚ultrasonography'/exp OR ultrasonography)) OR ‚ce ultrasonography' OR (ce AND (‚ultrasonography'/exp OR ultrasonography)) OR ceus OR ‚contrast-enhanced ultrasound'/exp OR ‚contrast-enhanced ultrasound' OR (‚contrast enhanced' AND (‚ultrasound'/exp OR ultrasound)) OR ‚contrast enhanced ultrasound'/exp OR ‚contrast enhanced ultrasound' OR ((‚contrast'/exp OR contrast) AND enhanced AND (‚ultrasound'/exp OR ultrasound)) OR ‚ce ultrasound' OR (ce AND (‚ultrasound'/exp OR ultrasound)))
898 -> Filters: Date: 2014-2024, Article, Study type: case report, case study, clinical article, clinical protocol, clinical study, comparative study, controlled clinical trial, controlled study, correlational study, cross sectional study, human, longitudinal study, multicenter study, multicenter study topic, observational study, phase 1 clinical trial, pilot study, prospective study, randomized controlled trial, retrospective study -> 411
411:
https://www.embase.com/#advancedSearch/resultspage/history.3/page.1/200.items/orderby.date/source.

Results of search summary:
All articles searched: 2303
All articles searched after filter: 883
Duplicates automatically detected: 471
Duplicates deleted: 284
First scanning (Rayyan): 599
The conflict between researchers: 2
Researcher 1: excluded 591, included 8, maybe 0
Researcher 2: excluded 589, included 10, maybe 0
Articles accepted for retrieval: 8
Articles removed after retrieval: 1 – not English, 1 – wrong study design
Articles rejected: 593
Articles included in study: 6

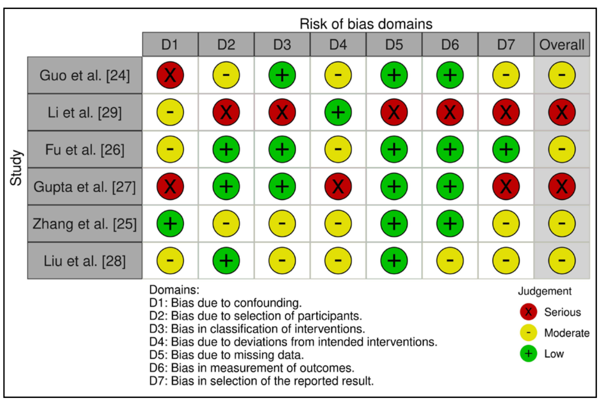
Results
Cohen's k: 0.8872

Almost perfect agreement

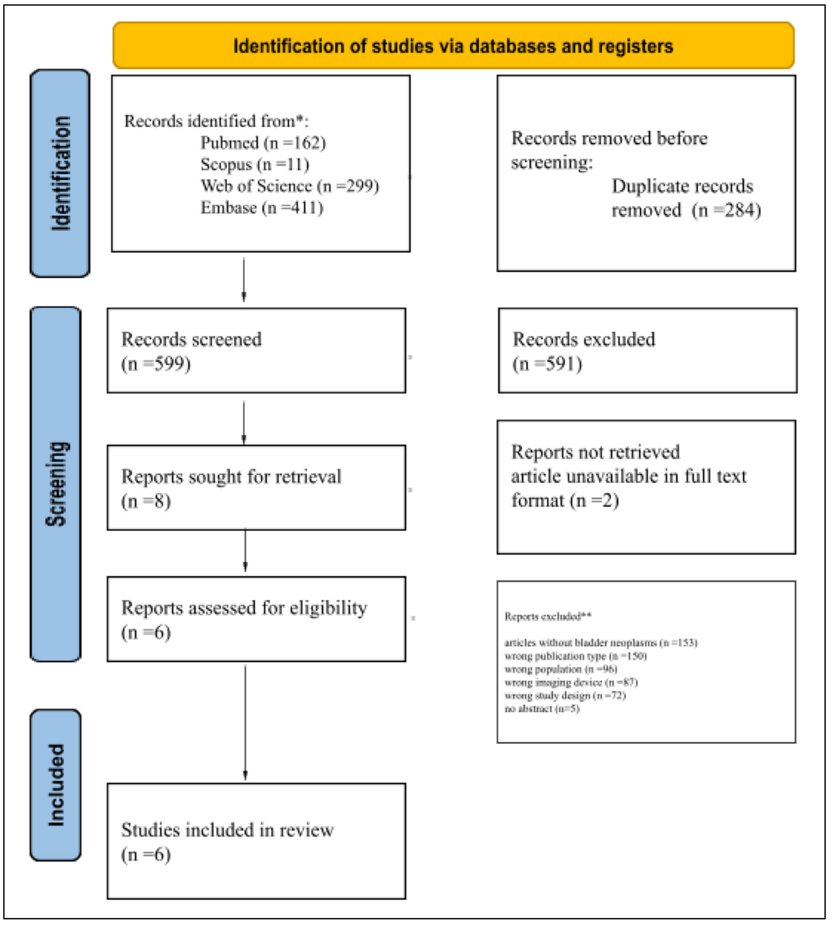
Supplement Table 1. *QUADAS-2 results*

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Guo et al. [24]	☹	☹	☺	☹	☺	☺	☺
Li et al. [29]	☹	☺	☺	☺	☺	☺	☺
Fu et al. [26]	☺	☺	☺	☺	☺	☺	☺
Gupta et al. [27]	☺	☺	☺	☺	☺	☺	☺
Zhang et al. [25]	☹	☺	☺	☺	☺	☺	☺
Liu et al. [28]	☺	☺	☺	☹	☺	☺	☺

☺ Low Risk ☹High Risk ? Unclear Risk



Supplement Figure 1. *Risk od bias domains.*



Supplement Figure 2. *PRISMA flowchart.*

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.
*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**Reports may have been excluded for more than one reason
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

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