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# CEUS in the differentiation between low and high-grade bladder carcinoma

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**KEYWORDS**
Contrast-enhanced ultrasonography, CEUS;
Bladder cancer;
Time-intensity curves;
Color-Doppler ultrasonography, CDUS.

**Abstract** *Introduction:* Bladder cancer ranks 4th overall in the number of newly diagnosed cancers and 10th in causes of cancer deaths. More than 90% of all cases of bladder cancer are transitional cell carcinoma (TCC). The goal of this study is to confirm the usefulness of low mechanical index contrast-enhanced ultrasonography (CEUS), also in association with time–intensity curves, in the differentiation between high- and low-grade bladder malignant lesions.
*Materials and methods:* From February 2006 to February 2012 we recruited 144 patients. All patients underwent grayscale ultrasonography (US), color-Doppler ultrasonography (CDUS) and contrast-enhanced ultrasonography (CEUS). Subsequently all patients underwent cystoscopy and TURB.
*Results:* Histological diagnoses were: 88 high-grade carcinomas (61.1%), and 56 low-grade carcinomas (38.9%). Sensitivity and specificity of CDUS were 87.5% (126/144) and 60%, respectively. Sensitivity and specificity of CEUS were 90.9% and 85.7%, respectively. Sensitivity and specificity of TIC were 91.6% (132/144) and 85.7%, respectively.
*Discussion and conclusions:* CEUS is a reliable noninvasive method for differentiating low- and high-grade bladder carcinomas since it provides typical enhancement patterns as well as specific contrast-sonographic perfusion curves.

**Sommario** *Introduzione:* Il carcinoma della vescica è al quarto posto complessivo per numero di tumori di nuova diagnosi e al decimo posto nelle cause di morte per cancro. Più del 90% di tutti i casi di cancro alla vescica sono dei carcinomi a cellule transizionali (CCT).Scopo di questo studio è stato quello di confermare l'efficacia dell'ecografia a basso indice meccanico con mezzo di contrasto (CEUS) anche con l'utilizzo di curve intensità-tempo (TIC) nella differenziazione tra lesioni vescicali di alto e basso grado.
*Materiali e metodi:* Da febbraio 2006 a luglio 2011 sono stati selezionati 144 pazienti. Tutti i pazienti sono stati sottoposti a ecografia in scala di grigi (US), ecocolor-Doppler (ECD) ed ecografia con mezzo di contrasto (CEUS). Successivamente tutti i pazienti sono poi stati sottoposti a cistoscopia e TURB.

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*Risultati:* Le diagnosi istologiche sono state: 88 carcinomi di alto grado (61.1%), e 56 carcinomi di basso grado (38.9%). La sensibilità e specificità dell'ECD sono state dell' 87.5% e 60%, rispettivamente. La sensibilità e specificità della CEUS sono state del 90.9% e 85.7%, rispettivamente. La sensibilità e la specificità delle TIC sono state del 91.6% e 85.7%, rispettivamente.
*Discussione e conclusioni:* La CEUS è una tecnica affidabile e non invasiva per differenziare i carcinomi della vescica di basso e di alto grado, in quanto fornisce dei pattern tipici di enhancement, così come specifiche risultano essere le curve intensità-tempo.
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## Introduction

Bladder cancer ranks 4th overall in the number of newly diagnosed cancers and 10th in causes of cancer deaths. More than 90% of all cases of bladder cancer are transitional cell carcinoma (TCC), with most of the remainder squamous cell carcinoma (5%), adenocarcinoma (2%), or rhabdomyosarcoma (1%). Thirty percent of patients with bladder tumors initially present with muscle-invasive or metastatic disease. Of these, 50% will die 2—3 years after the diagnosis despite aggressive local therapy. On the other hand, 70% of TCC are referred to as non-muscle-invasive or superficial bladder cancer at the initial presentation. These are tumors confined to the mucosa (70%) or lamina propria (30%). Approximately 50%—70% of these tumors will recur, with 10%—30% showing grade and stage progression [1-6].

Transurethral resection of bladder tumor (TURB) is the only procedure which allows the execution of a correct local staging. The goal of TURB is to enable a correct diagnosis by the pathologist, which means including bladder muscle in the adequately sized resection biopsies. The strategy of resection depends on the size of the lesion. Small tumors (less than 1 cm) can be resected *en bloc*, where the specimen contains the complete tumor plus a part of the underlying bladder wall including bladder muscle. Larger tumors have to be resected separately in fractions, which include the exophytic part of the tumor, the underlying bladder wall with the detrusor muscle and the edges of the resection area. At least the deeper part of the resection specimen must be referred to the pathologist in a separate labeled container to enable him to make a correct diagnosis. Furthermore the resection should include the removal of the bladder wall surrounding the lesion for at least 1 cm of diameter, to allow an assessment of eventual alterations of the mucosa [7—11].

Over recent years ultrasonographic contrast media have been used in order to assess the neoangiogenesis of these neoplasms; the goal of this study is to understand if it is possible to distinguish high-grade from low-grade lesions using specific contrastographic parameters, in order to provide better information for the execution of TURB [12].

## Materials and methods

From February 2006 to February 2012 we recruited 144 patients, age range 51—76 (mean age 68), 48 (33.3%) women and 96 (66.6%) men. Urinary cytology was positive in 96 (66.6%) of cases.

All patients underwent grayscale ultrasonography (US), color-Doppler ultrasonography (CDUS) and contrast-enhanced ultrasonography (CEUS). Subsequently all patients underwent cystoscopy and TURB. The time between CEUS and TURB was less than 15 days. Sonographic examination was performed on Technos Mpx, Mylab 70 Vx Gold (Esaote, Genova, Italy), and Toshiba Aplio VX (Osaka, Japan) using a 2—5 MHz multi-frequency broadband convex transducer. Examination was performed when the urinary bladder was adequately full (neither empty nor overfilled, but sufficiently full in order not to overestimate the lesions). For each session sonographic examination consisted of conventional grayscale imaging using tissue harmonic imaging (THI).

The location and size of the lesions detected during grayscale examination were recorded. CDUS was performed using scanning parameters set for maximum sensitivity to slow flow while the power output was increased to maximum. The color gain was increased until just prior to the appearance of random noise. The pulse repetition frequency was set at the lowest possible level.

All patients subsequently underwent real-time continuous examination using a low mechanical index (MI) (range: 0.04—0.1) after administration of SonoVue (Bracco, Milan, Italy). SonoVue was administered as an intravenous hand-injected fast bolus of 2.4 ml, followed by 5 ml of a saline flush. Images in the ideal scanning plane were displayed in real-time by slightly changing the scanning plane to portray the whole area of the lesion and the surrounding bladder wall. The true subtraction effect can be obtained only by using a low MI. This technique is based on signal amplitude subtraction (not only frequency subtraction) and is possible thanks to the combination of two different components: the harmonic signal coming from SonoVueTM and the dynamic threshold of low amplitude signals which suppress the low amplitude signals returning to the transducer.

The entire examination was digitally recorded with still images recorded on the optic disk. These images were subsequently reviewed on a frame-by-frame basis. The number, size, location and morphological features of the lesions were studied.

Quantitative analysis was subsequently performed using perfusion software.

TURB, executed by one operator, and the successive histologic exam lead to the finding of 8 high-grade Ta (5.6%), 56 low-grade Ta (38.8%), 72 high-grade T1 (50%) e 8 high-grade T2 (5.6%).

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