Purpose

Introduction

Cancer of the urinary bladder represents 6% of all malignancies in men, making it the 4th most common tumor. In women it represents 2% of malignancies. The main prognostic factors in urothelial cell carcinoma (UCC) are the depth of invasion and histological grade. When the tumor is confined to mucosa or lamina propria is considered superficial (represents 80% at diagnosis), when invades muscular layer or beyond is considered invasive (20% at diagnosis). Fig 1

Superficial tumors can be managed conservatively with local endoscopic resection with or without adjuvant administration of chemotherapeutic agents. Invasive tumors requires curative cystectomy or, in advanced stages, palliative chemotherapy or radiation therapy.

The 2004 World Health Organization (WHO) classification of non-invasive urothelial tumors, classifies in UCC low grade or UCC high grade. Between 30-50% of non-invasive urothelial tumors can be high grade and these presents worse prognosis.

According to the architecture of urothelial tumors can be classified as papillary and flat or solid tumors. Papillary tumors have better prognosis and are associated with low-grade superficial tumors. Low-grade papillary tumors confines to the mucosa appear to have only an increased risk of recurrence and almost no risk of progression. Solids or flat tumors are more commonly seen in high-grade cancers and in association with carcinoma in situ and potentially invasive.

Transabdominal ultrasound, CT and MRI have been used for staging of bladder cancers but none of these techniques is sufficiently accurate. The reported staging accuracy of CT is limited (40-60%). The notable advantage of MRI with contrast is its apparent ability to differentiate between superficial and muscle-infiltrating tumors but overstaging is a common problem. Contrast-enhanced ultrasound (CEUS) has been used to determine wall depth infiltration by evaluating enhanced wall pattern. After contrast administration the layers can be differentiated, especially submucosal layer and tumor tissue displays an intense enhancement in the arterial phase owing to increased contrast resolution between the tumor and the muscular layer.

High-grade tumors have an intense neoangiogenesis that can be assessed by different dynamic contrast techniques. CEUS can demonstrate and quantify neoangiogenesis. The use of quantitative methods allows acquire signal-intensity curves and analyses the rate of enhancement, wash-in and wash out curve, and perfusion parameters.

Purpose
To determine the usefulness of contrast-enhanced ultrasound in estimating the degree of infiltration of bladder tumor

To assess the contrast-enhanced ultrasound ability to predict histologic grade

**Images for this section:**

![Diagram showing stages of tumor invasion in urothelial cell carcinoma.](image)

**Fig. 1:** Diagram shows the stages of tumor invasion in urothelial cell carcinoma.
Methods and Materials

The study was prospectively performed on patients with bladder cancer diagnosed by ultrasound or cystoscopy. In each patient, one or two lesions were studied by contrast-enhanced ultrasound, we choose most likely to infiltration or larger lesion. 30 lesions in 26 patients were studied.

IMAGING ANALYSIS

**Grayscale conventional US**

We evaluated the location, size a number of lesions. They were classified according its morphology as sessile, polipoid or plaquelike.

One or two lesions were chosen for CEUS, preferably those with infiltration wall suspected.

**CEUS**

We analyzed the behavior after contrast and quantitative analysis was performed using perfusion software.

**Wall infiltration:**

- Considered **non invasive tumor** if there was evidence of a hypoechoic layer between the lesion and adjacent bladder wall and **invasive tumor** with the absence of a hypoechoic layer between the lesion and adjacent bladder wall at base of tumor and presence of disruption of the muscle layer by enhancing tumor tissue.
- We performed a subjective scale of wall infiltration: no (non infiltration), indeterminate (presence or absence of muscle infiltration could not be determined), yes presence of muscle infiltration).

**Brightness-time curve:** We used a program that analyzes the perfusion time sequence of images and calculates the time-intensity curve by the position of a ROI in the lesion area next to the wall.

The parameters analyzed were:

- Time to peak (it was the time needed to reach maximum value)
- Enhancement percent rate
- Morphology of the washing curve (slow or fast)
HISTOLOGYC EXAMINATION

Transurethral resection (TUR) or radical cystectomy was made at 24 or 48 hours after contrast-enhanced ultrasound. In the cystoscopy it was considered number, location and morphology of the lesions and the infiltration of muscular layer.

In the histopathologic study we pay attention to histological grade, appearance (solid or papillary) and the invasion or not of the lamina propria and muscular layer.

STATIDTICAL ANALYSIS

The Pearson chi-square and Mann-Whitney test was used to assess the relationship between the brightness-time curves, appearance and histological grade. The concordance between the contrast ultrasonography and histology was calculated.

Results

Seventeen of the 30 tumors were limited to the mucosa, 3 were infiltrating. Ten lesions could not be classified due to lack of muscle tissue in the sample.

The histological diagnosis showed 18 low-grade papillary tumors, 6 high-grade papillary tumors and 4 high-grade solid tumors (2 lesions not analyzed by cauterization of the sample). Fig. 2 on page 6

Contrast-enhanced ultrasound showed infiltration in all invasive tumors (3 true positives) Fig. 3 on page 9 and no infiltration of 14 of the 17 superficial (14 true negatives) Fig. 4. Sonographic grade of depth invasion could not be determined in 3 cases of superficial tumors. Fig. 5 on page 10. There was a correct diagnosis in 85% of cases. Fig. 6 on page 7

In the analysis of the curves, high grade and solid tumors showed a shorter time to peak. Fig. 7 on page 11

The slope of the enhancement curve in low-grade and papillary tumors was greater than in high grade and solid tumors. Fig. 8 on page 12 Fig. 9 on page 13

When analyzing the washout curve, high grade and solid tumors showed faster washout. Fig. 10 on page 14 Fig. 11 on page 15
In terms of enhancement percent rate no significant differences were found.

Images for this section:

**Fig. 1:** Diagram shows the stages of tumor invasion in urothelial cell carcinoma.
Fig. 2: Tables with the level of invasion and histological grade in the 30 lesions analyzed
Fig. 6: Correlation between CEUS infiltration classification and pathology results
Fig. 4: a) Grayscale US shows a left polypoid ureteral meatus lesion, b) On CEUS, the same lesion shows intense enhancement and the presence of a hypoechoic depth layer (red arrow) that represents the muscular layer. The anatomopathological diagnosis was a low-grade superficial papillary lesion without infiltration of lamina propria or muscle layer.
**Fig. 3:** CEUS study shows polypoid lesion with obvious infiltration beyond the muscle layer (yellow arrow). The diagnosis of high-grade invasive solid UCC was performed by histological study.
**Fig. 5:** CEUS study shows sessile lesion with doubtful loss of hypoechoic layer (red arrow), classified as Indeterminate lesion. In the histological study the muscle layer invasion was not identified and the diagnosis of low-grade superficial papillary UCC was made.
**Curves Brightness-time analysis**

1. **Time to peak** (Elapsed time from initial uptake to peak of maximum enhancement)

<table>
<thead>
<tr>
<th>Morphological type relationship with time to peak (sec)</th>
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<tbody>
<tr>
<td>Papillary</td>
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<td>Solid</td>
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<table>
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<tr>
<th>Histologic grade relationship with time to peak (sec)</th>
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<tbody>
<tr>
<td>Low-grade</td>
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<tr>
<td>High-grade</td>
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</table>

**Fig. 7:** The statistical results of the relationship between time to maximum enhancement and morphologic and histologic grade
**Fig. 8:** Curves Brightness-time analysis in low grade papillary tumor (a) and high-grade solid tumor (b). The low grade tumors showed longer time to peak (slow slope) that high grade tumors (fast slope).
**Fig. 9:** The statistical results of the relationship between washout curve enhancement (fast or slow) and morphologic and histologic grade

<table>
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<th>Slow (n)</th>
<th>Fast (n)</th>
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<tbody>
<tr>
<td><strong>Morphological type relationship with washout curve morphology</strong></td>
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<td>Papillary</td>
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<tr>
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</table>
Fig. 10: Washout curve in a low-grade papillary tumor shows a slow decline in the curve (yellow line)
Fig. 11: Washout curve in a high-grade papillary tumor shows a fast decline in the curve (yellow line)
Conclusion

- Contrast ultrasonography showed significant differences in the morphology of the washout curve between the different histological grades (high or low grade) and between the various morphological patterns (solid-papillary).

- With regard to wall invasion it can make a correct diagnosis in a high percentage of cases (85%).

- Therefore, this technique can be a useful tool in the management of bladder lesions. However more studies are needed with longer time series for confirmation.

References


Personal Information