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Accuracy of modern ultrasonographic techniques in the follow up of patients with superficial bladder carcinoma

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Abstract

Purpose: The present study was carried out to establish the accuracy of modern ultrasonographic techniques in the follow up of patients with superficial bladder carcinoma and to evaluate the patients tolerability of cystoscopy. **Methods:** Thirty three patients with a history of superficial bladder carcinoma under active surveillance were initially examined using transabdominal ultrasound followed in the same day by cystoscopy. **Results:** Fourteen out of the 33 subjects were found to have bladder carcinoma recurrence on cystoscopy. In 11 cases (78.57%) US accurately diagnosed the bladder carcinoma. Two out of the 3 patients in which, the US examination failed to clearly diagnose bladder carcinoma, were found with a tumor smaller than 3 mm while, in the remaining patient the tumor was located in the inner part of a diverticula. The sensitivity of modern ultrasonographic techniques in the diagnosis of bladder cancer recurrence was 78.5%, the specificity 100%, the positive predictive value 100% and the negative predictive value 86.3%. Regarding the patient tolerability for cystoscopy, 17 patients (51.5%) reported excessive discomfort-low tolerability, 9 (27.2%) moderate discomfort-intermediate tolerability and 7 (21.2%) reported no discomfort-high tolerability. **Conclusion:** The technological evolution has rendered ultrasonography more accurate in the diagnosis of bladder carcinoma and thus it can be incorporated in the follow up schedule of patients with superficial bladder carcinoma.

Keywords: bladder, neoplasms, ultrasonography, cystoscopy.

Rezumat

Scopul studiului a fost de a stabili acurateţea tehnicilor moderne de ecografie în urmarirea pacienţilor cu carcinom superficial al vezicii urinare şi de a stabili tolerabilitatea pacienţilor la manopera de cistoscopie. **Material şi metodă:** In aceiaşi zi au fost examinaţi 33 de pacienţi cu istoric de carcinom vezical aflaţi în supraveghere activă, iniţial prin ecografie transabdominală urmată de cistoscopie. **Rezultate:** 14 pacienti au fost identificaţi ca având recurenţă a carcinomului vezical. La 11 dintre aceştia (78,57%) ecografia a diagnosticat corect tumora. La doi dintre cei 3 pacienţi nediagnosticaţi ecografic tumora a fost sub 3 mm iar la al treilea pacient tumora a fost situată în partea internă a unui diverticul. Sensibilitatea tehnicilor ecografice moderne în diagnosticul recurenţelor cancerului vezical a fost de 78,5%, specificitatea de 100%, valoarea predictivă pozitivă de 100% iar cea negativă de 86,3%. In ceea ce priveşte tolerabilitatea pacienţilor la cistoscopie 17 pacienţi (51,5%) au avut discomfort excesiv-tolerabilitate joasă, 9 (27,2%) discomfort moderat-tolerabilitate intermediară iar 7 (21,2%) nu au raportat discomfort şi au avut tolerabiliate înaltă. **Concluzii:** Prin achiziţiile tehnologice recente ecografia a devenit o tehnică acurată în diagnosticul cancerului vezical şi din acest motiv ar putea fi inclusă in protocolul de urmărire a pacienţilor cu cancer vezical superficial.

Cuvinte cheie: vezica urinară, cancer, ecografie, cistoscopie

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The typical recommendation for active surveillance in superficial bladder cancer is based on repeat cystoscopies (CS). CS directly visualizes lower urinary tract anatomy and macroscopic pathology, and can determine if the hematuria originate from the urethra, bladder, or from the upper urinary tract. In addition, material for cy-

tological and histological examination can be obtained using CS techniques [1]. For the above reasons, CS is considered to be the gold standard in the follow up of the superficial bladder cancer recurrence [1]. However, CS is invasive, time-consuming and expensive. Sedation is frequently necessary, and iatrogenic injury to the urethra and bladder as well as infection may occur [1]. On the other hand, modern sensitive transducers have improved the imaging of the urinary tract rendering trans-abdominal ultrasonography (US) more effective in visualizing intraluminal filling defects in the bladder than it was in the past. Moreover US is a non invasive, well accepted, cost effective diagnostic method [2]. Some investigators argue that often CS is not always needed and suggest the systematic use of US alone or in combination with urine cytology, to follow up the superficial bladder cancer recurrence [3-5].

To our knowledge, up to now no trials comparing the accuracy of modern US techniques with that of CS in the diagnosis of recurrence of superficial bladder carcinoma were performed and there is only one paper concerning the patient's tolerability and acceptance level of urological endoscopic procedures [6].

The present study was carried out to study prospectively the accuracy of trans-abdominal US in the follow up of superficial bladder carcinoma. Taking for granted patients' tolerability undergoing a trans-abdominal US procedure, we evaluated also the patients' tolerability of CS. Our final objective was to evaluate the accuracy of the systematic use of US to follow up the superficial bladder cancer.

Materials and methods

This controlled prospective study took place at the General Hospital of Thebes (Viotia, Greece) from April 2006 to November 2006 and at the "Tzaneion" General Hospital (Pireas, Greece) from September 2008 to February 2009. The study group included a total of 45 patients who had a recent history of recurrent superficial bladder cancer and subsequent transurethral resections of bladder tumor (TUR-BT). Inclusion criterion was the established diagnosis of superficial bladder carcinoma confirmed in the pathology report of previous TUR-BT. The exclusion criterion was the previous diagnosis of the carcinoma in situ which is not visible on radiological imaging techniques. All patients were initially investigated by trans-abdominal ultrasound. Urinary tract abdominal US examination was performed with full bladder. Patients who presented blood casts in the urine sample underwent transurethral catheterization and bladder lavage.

Nineteen subjects were investigated in the radiology department of General Hospital of Thebes with a GE Logiq 3 Pro (GE Ultraschall, Deutschland GmbH & Co. Solingen, Germany) with convex array (2-5 MHz) and linear array (3-6.7 MHz). The remaining 26 were investigated in the radiology department of Tzaneion General Hospital. Of them 10 were examined with a Hitachi EUB 8500, (Hitachi Medical Systems, Europe), with convex array (2-5 MHz) and linear array (6-13 MHz) probes and 4 with an Esaote Megas GPX, (Esaote Biomedica, Genoa, Italy) with convex array (2-5 MHz) and linear array (5-7 MHz) probes. Two different consultant radiologists performed urinary tract ultrasonography.

Urinary bladder was scanned at sagital, axial and oblique planes with convex probes. In selected cases linear probes were used to assess small lesions at the dome of the distended bladder. Several modern facilities (Depth, Gain, Focus Harmonics, Virtual Convex, 3D reconstruction) (fig 1-3) were used in order to maximize the likelihood of the detection of small lesions. Color or spectral Doppler imaging was also performed in order to distinguish tumors from adherent clots and to determine if a bladder mass was vascularized and therefore arising from the bladder wall. Color Doppler parameters (filter, gain, PRF) were optimized for detection of slow flow in small vessels. The main diagnostic criterion for the US diagnosis of superficial bladder cancers was the presence of irregular soft tissue structures of low – to intermediate-echo texture projecting into the bladder lumen from a fixed mural site.

CS was performed immediately after by two consultant surgeons. Rigid cysteoscopes sized from 16 to 25 Fr were used for the examination of the bladder mucosa. An Olympus 30° lense was used in the surgery department of the General Hospital of Thebes, while a Karl Stortz 30° lense was used in the urology department of Tzaneion

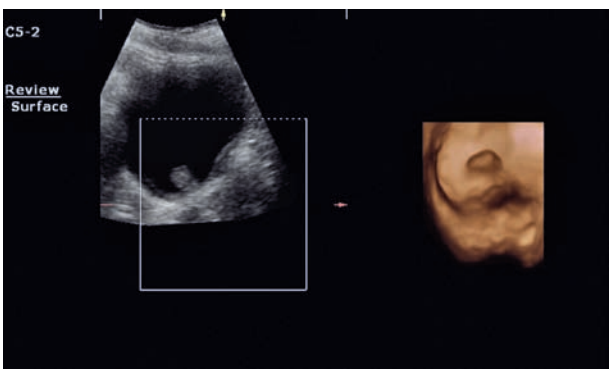


Fig 1. Sonographic detection of a recurrent bladder tumor, arising from the posterior wall of the urinary bladder (sagittal section) and the 3-dimensional sonographic reconstruction of the lesion.

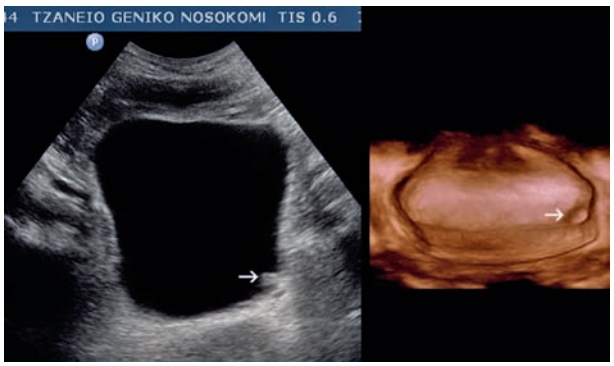


Fig 2. Sonographic detection of a relatively small recurrent bladder tumor, with a diameter of 6 mm, arising from the left posterolateral wall of the urinary bladder (axial section) and the 3-dimensional sonographic reconstruction of the lesion (arrows).

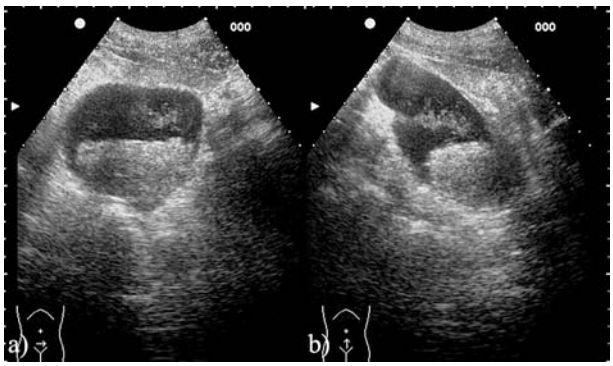


Fig 3. Transverse (a) and longitudinal (b) scan of an adherent clot: hyperechogenic material occupies the dependent portion of the urinary bladder. Although the location, the echogenicity of the finding and the presence of "layering" are suggestive of a blood clot, a coexistent tumor could not be safely excluded by imaging alone. Most of this material showed no movement when turning the patient (attached clots).

General Hospital. None of the urologists were aware of the ultrasound examination findings.

Immediately after cystoscopy, all subjects underwent a self-assessment survey for the acceptance of the procedure and were asked whether they were prepared to take the test again if necessary and how many CS's they had undergone in the past. Each subject was provided with an optical pain-meter scaled from 0 to 10 to measure discomfort or pain level of CS (1-3 excessive discomfort-low tolerability, 4-7 moderate discomfort-intermediate tolerability, 8-10 no discomfort-high tolerability).

A similar registration form was used for recording findings of US and CS of each patient. In all cases the images recorded have been reviewed to reach a consensus. Findings of bladder US such as number, size and location of lesions, were correlated with those visualised by CS. Subjects with US and/or CS findings suggestive of bladder carcinoma were further evaluated and treated: TUR-BTs and histopathological analyses were performed in the Tzaneion Hospital of Pireas. Confirmation of the bladder carcinoma was achieved by the histopathogical examination of the submitted specimens of bladder biopsy in each case.

Statistical analysis was performed using Fisher's exact test of significance. The accepted level of significance in this study was 0.05 (P value <0.05 is significant).

The locally appointed Ethics Committees approved the research protocol, while all subjects were informed and signed the informed consent from. The administration of the General Hospital of Thebes supported the study financially.

Results

From a total of 45 patients initially enrolled, 9 discontinued the study and were excluded from it. Three out of the 36 selected patients had a diagnosis of carcinoma in situ in the histopathology report of TUR-BT and were excluded from the study also. The remaining 33 patients who fulfilled the inclusion criterion finally comprised the study group.

The age of the examined subjects ranged from 56 to 81 years (average 74 years, median 67 years). Twenty nine subjects were male. Patients were classified according to the pathology reports of the previous TUR BTs obtained from the medical files of these 33 patients in 3 groups. The Group A consisted of patients at low risk of recurrence and progression (16 patients) while Group B consisted of patients at high risk of progression (7 patients) and Group C comprised patients at an intermediate-risk of progression (10 patients).

Upon the completion of the study, 14 out of the 33 subjects -all males-were found to have bladder carcinoma recurrence [6 patients of the group B (85.7%), 5 of the group C (50%) and 3 patients of the group A (18.7%)]. One out of the 7 patients at high risk of progression was found with a muscle invasive tumor.

According to the statistical analyses, the difference in recurrence rate between the groups A and B is statistically significant (The two-tailed P value equals 0.0049). In contrast, the difference in recurrence rate between the groups B and C is considered to be not statistically significant (the two-tailed P value equals 0.3043).

Eleven subjects were found with abnormal bladder

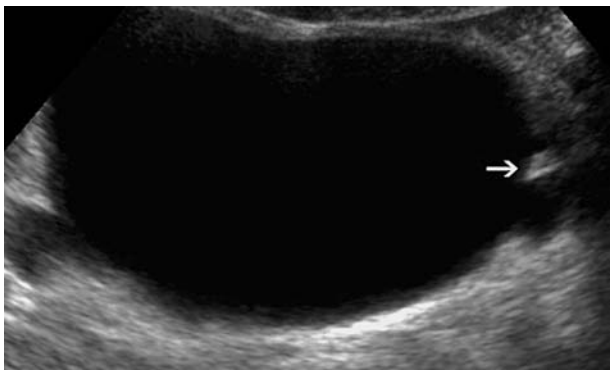


Fig 4. Tumor located in the inner part of a diverticulum (arrow).

Table I – Misdiagnoses of ultrasonography in the detection of bladder carcinoma

	Number	Rate
Interobserver variations	2	2/2 (100%)
False positive findings	1	1/2 (50%)
False negative findings	3	2/2 (100%)

US (78.57%). Two out of the 3 patients in which, the US examination failed to clearly diagnose bladder carcinoma, were found with a tumor smaller than 3 mm during the CS procedure (both of the Group A), while, in the remaining patient (of the Group B) the tumor was located in the inner part of the diverticulum (fig 4). In two cases, radiologists suggested different diagnoses regarding the size and number of tumours (interobserver variation). Finally, in one case a false-positive finding was recorded by one observer (table I).

According to our findings the sensitivity of modern ultrasonographic techniques in the diagnosis of bladder cancer recurrence is 78.5%, the specificity is 100%, the positive predictive value100% and the negative predictive value 86.3%.

In response to the patient tolerability for CS 17 subjects (51.5%) reported excessive discomfort-low tolerability, 9 (27.2%) reported moderate discomfort-intermediate tolerability and 7 (21.2%) reported no discomfort-high tolerability. All patients, apart from one, said that they would undergo the test again if necessary.

Discussion

Bladder cancer comprises a heterogeneous group of tumours, the majority of which are non-muscle-invasive carcinomas. At diagnosis, 60-80% of tumours are superficial and endoscopic resection is the initial treatment for this disease. In patients with low, medium or high risk disease, about 20%, 40% and 90%, respectively, will develop tumour recurrence [7]. To delay or prevent recurrence, intravesical therapy is routinely used however controversy exists as to which agent and schedule should be used. Tumor numbers, shape, size, stage and grade are significant recurrent and prognostic factors [8]. Moreover, recurrence depends on appropriate tumor resection as well as on patients' adherence to the adjuvant treatment [9].

The unexpected 42% recurrence rate (14 of 33 patients) found in our study is unusually high, given that it actually represents the recurrences in the time between two cystoscopies. Reasons explaining this finding are practically unknown. It could be hypothesised that it may be due to the relatively large number of high risk bladder cancer patients (7 patients). Another reason explaining the relatively high recurrence rate is the fact that almost half of low risk patients did not have an immediate single postoperative instillation of chemotherapy agent after complete transurethral resection of the tumor as it was not mandatory at that time). Interestingly, all patients are from the cities of Thiva, Inofyta and Schimatari, (Thiva-Tanagra-Malakasa basin, Eastern Sterea Ellada, Greece), which supports many industrial activities. Concentrations of chromium [up to up to 80 μg/L Cr(VI)] were recently found in the urban water supply of Inofyta city. Cr(VI) concentrations ranging from 5 to 33 μg/L Cr(VI) were found in groundwater that is used for Thiva's water supply. Arsenic concentrations up to 34 μg/L along with Cr(VI) levels up to 40 μg/L were detected in Schimatari's water supply [10]. The use of drinking water contaminated by hexavalent chromium and other heavy metals from industrial discharges has been associated with carcinogenesis [11,12].

Almost 50% of patients with superficial bladder cancer are patients with low risk bladder tumours and in the vast majority of cases the recurrent tumor is of the same stage and grade as the primary tumor. As also shown in our study, patients with low risk bladder tumours have a very low risk for progression and a sparse recurrence rate. Therefore, aggressive surveillance is possibly not necessary and certainly can be bothersome [13]. Attempts to modify the standard approaches to surveillance for patients with superficial diseases were focused more on the monitoring schedule than on the diagnostic tools. In the past, CSs were uniformly performed every 3 months for

the first year, every 6 months for the second year, and yearly thereafter. Current guidelines are sparing patients from CS's who are at low risk of recurrence and progression [6]: if the initial CS is negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years. In contrast, patients with tumours at high risk of progression should have a cystoscopy every 3 months. If negative, the following CS's should be repeated every 3 months for a period of 2 years, every 4 months in the third year, every 6 months thereafter until 5 years, and yearly thereafter. Patients with intermediate-risk of progression (about one-third of all patients) should have an in-between follow-up scheme using cystoscopy and cytology, adapted according to personal and subjective factors [6].

Interestingly, the abovementioned recommendations are not based on evidence-based data but on retrospective experience (Grade of recommendation: C) and often the decision to work up a patient for urinary tract malignancy can be complicated [14].

However, there is a paucity of prospective data examining alternative follow-up methods. US constitutes a simple and quick examination which it is not associated with any complication inherent to CS and can be safely performed on all individuals with no restrictions e.g. elderly patients, disabled patients who cannot undergo CS, etc. US is also easily available, cost effective and a non-invasive technique requiring no special preparation, providing images of both the upper and lower renal tract. In the past, various authors have proposed the use of non invasive imaging tests in the initial investigation for detection of bladder carcinomas [15,16]; however, due to the lower accuracy of the existing devices, US has been accused as not being an appropriate method for the follow up of bladder cancer [17].

Technological evolution of ultrasound devices has increased the diagnostic accuracy of this examination. In fact, current scanners -that combine several different transducers and color or spectral doppler imaging facilities- are more accurate in the visualization of intra-luminal filling defects of the bladder than they was before [18]. In our study, a well performed ultrasonography provided important information of the condition of the urinary bladder in most of the cases and accurately detected the 78.5% of bladder carcinoma recurrences. Furthermore, in three patients, abnormality in the upper urinary tract secondary to ureteric involvement by bladder carcinoma has been also revealed. Despite the remarkable improvements in the diagnostic accuracy, some of the pitfalls of US test for evaluation of the bladder still remain. Smaller lesions (smaller than 0.5 cm) and lesions located in the dome or bladder neck are more difficult to visualize sonographically. Tumor configuration is also an important factor: plaque-like lesions are almost certainly harder to detect than polypoid ones [19]. Notably, in our study, the smallest carcinoma detected was 4 mm in size; while ultrasound failed to clearly diagnose bladder carcinoma smaller than 3 mm. Accurate detection also depends on the experience and skill of the person performing the study. The US technique might also lead to misdiagnosis due to external factors, such as obesity and degree of bladder distension [11]. Despite the abovementioned pitfalls, since a skilled operator easily overcomes such difficulties, US still remains a useful diagnostic tool for the follow up of patients with superficial bladder carcinoma treated with TUR-BT.

On the other hand, CS is invasive, expensive, time-consuming, not deprived of complications, and is not always a well-tolerated procedure and moreover is known as a painful diagnostic procedure [3]. Actually, the idea of having a CS may make a patient feel nervous, embarrassed, or scared. By explaining why the visit is necessary, giving the patient a sense of what to expect, and addressing any questions or fears he might have, it may help him feel more comfortable about taking this step.

As it is clearly shown in our study, vast differences in discomfort level between patients are possibly due to the prejudice against an invasive method: the more CS's the patients underwent in the past, the less discomfort they feel. However, CS being a painful diagnostic procedure is not always tolerated by the patients and several patients interrupt the cystoscopy surveillance [20]. Although most superficial bladder cancers are less likely to harm the patient if left undiagnosed and untreated, according to our belief is maybe unethical not to follow up closely such conditions. Since diagnosis of bladder cancer requires histopathological confirmation ultrasonography is certainly not the most adequate examination for the diagnosis of the recurrence of bladder carcinoma. However, based on our findings we suggest that the follow up schedule of patients with low and intermediate superficial bladder carcinoma should include more often ultrasonographies. Patients diagnosed to be suffering from bladder carcinoma recurrence by ultrasonography should be scheduled directly and promptly for cystoscopy and bladder tumour resection.

Conclusions

Technological evolution has rendered ultrasonography more accurate in the diagnosis of bladder carcinoma. On the perspective of the authors, while CS (and biopsy) remains the gold standard, ultrasonography represents a valuable tool in the initial radiological investigation for

detection of bladder carcinomas recurrence. Since the visualisation of a bladder tumour in earlier imaging can save money and time, the follow up schedule of patients with intermediate and low risk superficial bladder carcinoma should include more often ultrasonographies.

Conflict of interest: absence of conflict of interest

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