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Comparison of Virtual Cystoscopy and Transabdominal Ultrasonography with Conventional Cystoscopy for Bladder Tumor Detection

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Abstract

Purpose: We compare virtual cystoscopy (VC) and transabdominal ultrasonography (US) with conventional cystoscopy (CC),the gold standard, for detection of bladder tumors.
Patients and Methods: Forty-five patients suspected to have bladder neoplasms were evaluated prospectively. They underwent transabdominal US, followed by VC and CC. We compared sensitivity and specificity of US and VC and their positive and negative likelihood ratios. US and VC detection rates for tumors ≤ 1 cm and tumors larger than 1 cm were compared. Histologic grade and multiplicity were correlated to detection rate.
Results: In the study population of 33 men and 12 women, mean age was 67.1 ± 10.9 years. Thirty-nine lesions were observed on VC and 26 lesions were observed on US of the 41 neoplasms detected at CC. Transitional bladder cancer was present in 75.6% of cases, chronic cystitis in 9.75%, endometriosis in 4.9%, and other conditions accounted for 9.75%. Thirty-one tumors were polypoid and nine were sessile; 61% were larger than 1 cm and 39% were ≤ 1 cm. Both US and VC 91.2% specificity, but sensitivity was better for VC (95.1%) than for US (63.4%). Multiple tumors had a better detection rate by both methods ($P < 0.001$). Histologic grade was positively correlated to detection rate for US ($P < 0.01$) but not for VC. VC was more accurate in detection of polypoid tumors compared with US ($P < 0.05$).
Conclusions: VC showed better accuracy for detection of bladder neoplasms, especially in tumors smaller than 1 cm and for polypoid lesions.

Introduction

BLADDER PATHOLOGIES encompasses a wide group of conditions, including neoplasms, inflammation, infection, stones, and other abnormalities. Clinically, patients with these conditions present with hematuria, dysuria, and voiding symptoms.[1] Today, with routine use of imaging in daily practice to evaluate abdominopelvic, urologic, and gynecologic conditions, incidental tumors comprise a bigger percentage of cases referred to the urologist.

Different noninvasive methods are used for diagnosis, with ultrasonography (US) being the most used in daily practice. Virtual cystoscopy (VC) has been applied recently to study bladder tumors.[1–9] It consists of three-dimensional (3-D) computer-rendering techniques with the possibility of interactive intraluminal navigation through the bladder simulating conventional cystoscopy (CC).

CC remains the gold standard for bladder tumor detection and follow-up. In this procedure, visualization and resection of bladder tumors and biopsy of all suspected areas and lesions can be performed. It has drawbacks, however, such as invasiveness, discomfort to the patient, high costs, iatrogenic injury, and urinary sepsis.[1–9] Because some lesions, such as those of bladder cancer, usually recur, necessitating long-term follow-up, an accurate imaging method would help to reduce the number of CC procedures.

The aim of our study was to compare pelvic US and VC for detection of bladder tumors with CC.

Patients and Methods

Between July 2002 and September 2006, 45 patients (33 men and 12 women: mean age 67.1 ± 10.9 years; range 41–81 years) in whom bladder neoplasms were suspected were

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evaluated. Written informed consent was obtained from all patients. According to our service protocol, patients underwent pelvic US, followed by VC. Each person underwent CC after US and VC to confirm diagnosis. Seventy-five complete analyses were obtained.

All patients underwent transabdominal bladder US in the supine position with a full bladder. For that procedure, they drank about 900 mL of water 1 hour before the examination.

Longitudinal, transverse, and oblique scans were obtained using a model Logiq 5 (GE Healthcare, Milwaukee, WI) or HDI 5000 (ATL Bothell, WA,) unit and convex 2.5–5.0 MHz transducers and were all performed by a board-certificated radiologist (LN) with more than 10 years' experience in transabdominal US. The sonographer evaluated the bladder—its walls, looking for focal or diffuse lesions, and also its contents (Fig. 1A).

For VC, a urethral catheter was placed in the bladder, all urine was drained, and the bladder was insufflated with approximately 250 to 350 mL of room air (or to tolerance). With the use of Siemens Somaton Plus Volume Zoom helical scanner (scanning parameters: thickness 1.0 mm; increments 0.5 mm; mAs 95; kVp 120; table speed 0.5 second per 360-degree rotation; pitch 6.0) and holding of a single breath, a CT scan of the air-distended bladder was obtained with the patient in the supine and prone positions to avoid any lesion that was missed because of residual urine. Sequences lasted approximately 12 seconds.

The data were then transferred to a workstation (Virtuoso software, Silicon Graphics) for 3-D virtual reconstruction and image analysis. Initially, segmentation of axial images was performed, and bladder wall irregularities, focal or diffuse thickness, and polypoid or sessile lesions were investigated, together with extravesical involvement (Fig. 1B).

After that, 3-D perspective volume-rendering algorithms were used to generate intraluminal views of the bladder. 3-D virtual reconstruction was performed to search for any

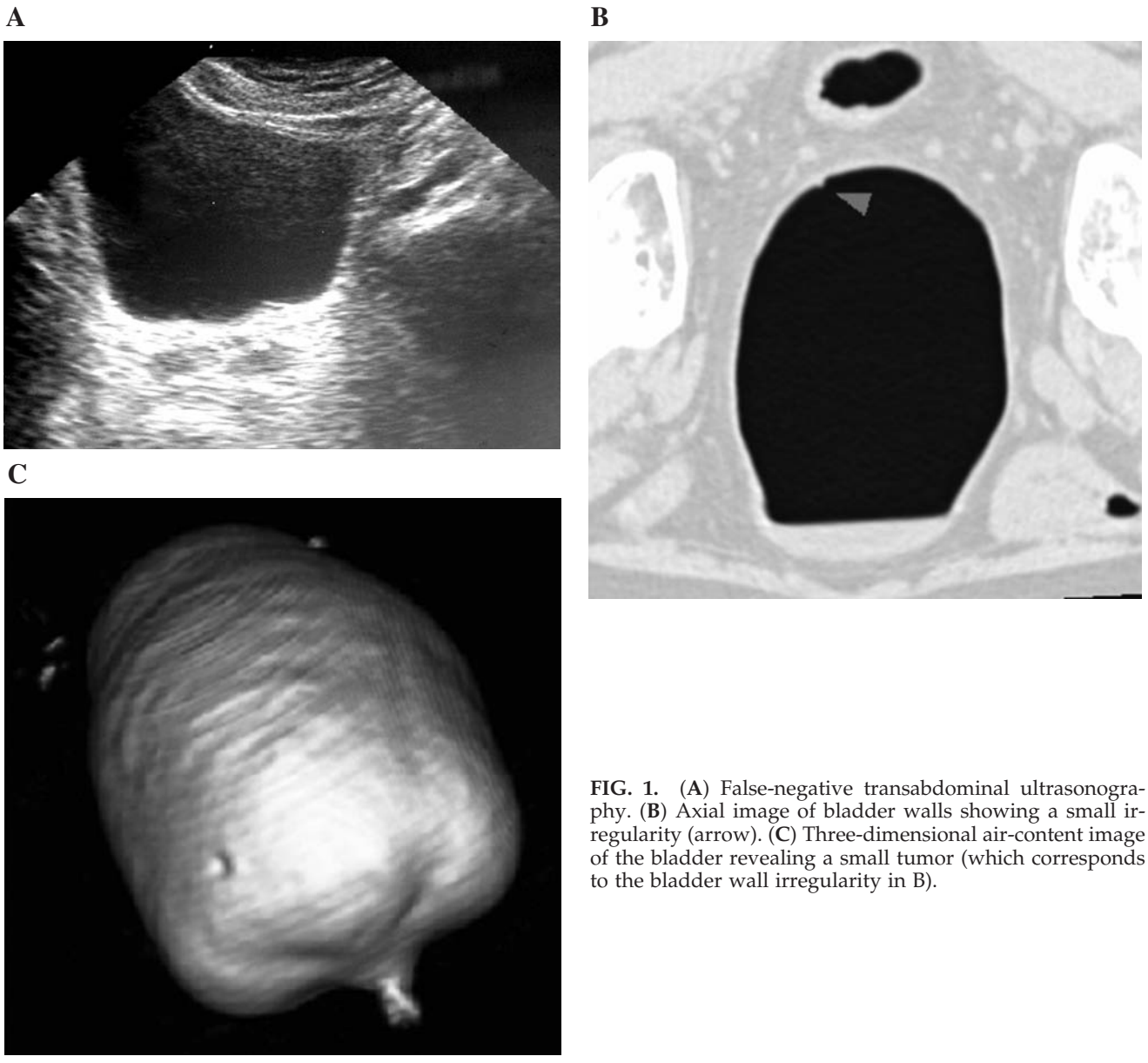

FIG. 1. (**A**) False-negative transabdominal ultrasonography. (**B**) Axial image of bladder walls showing a small irregularity (arrow). (**C**) Three-dimensional air-content image of the bladder revealing a small tumor (which corresponds to the bladder wall irregularity in B).

missed tumor. A 3-D search for tumors consisted of virtual navigation, looking for bladder wall irregularities and then creation of a subtraction image of the bladder to visualize if a bladder tumor had produced a negative image on the air content filling the bladder (Fig. 1C). VCs were all performed by a board certificated radiologist (CA) with more than 10 years' experience in abdominal CT.

CCs were performed with a rigid 21F cystoscope (Storz, Germany) with a field of 30 degrees. All patients received general anesthesia or raquianesthesia. All CCs were performed by a board certificated experienced urologist (RNL) with more than 30 years' of urologic expertise.

Each examination was conducted by a different person (LN, US; CA, VC; RNL, CC) who was unaware of the results of the other investigators. Data acquisition of US, VC, and CC findings, tabulation, statistics, and results interpretation were performed by the other two investigators (RIL and DYT).

Clinical presentation and indication for radiologic evaluation were obtained in all patients. Presence of tumor, tumor histology, tumor size, site, multiplicity, type, (polypoid versus non-polypoid) and tumor grade (1–4) were evaluated in all examinations. Subsites, grades, and histologic classifications were those designated by the World Health Organization, as outlined in the International Classification of Diseases for Oncology (ICDO), 1976. Subsites were trigone, dome, lateral walls, anterior wall, posterior wall, neck, and ureteral orifices. The ICDO grade 1 and 2 tumors were considered low grade and grade 3 and 4 tumors were considered high grade.[10] The lesions were classified as sessile (nonpolypoid) when they had a broader base compared with their height, and as polypoid when the neoplasms were taller than wider at their base.

Sensitivity, specificity, and positive (PLR) and negative likelihood ratios (NLR) were calculated for US and VC and compared. Sensitivity and specificity were compared using the Wilson score method and likelihood ratios were compared using the Simel method. The Newcomb-Wilson method was used to compare US and VC for tumors ≤ 1 cm in diameter and tumors larger than 1 cm. the chi-square test and Spearman correlation were used, respectively, to identify if multiplicity and histologic grade were positively correlated to the detection rate.

Results

Indications for radiologic investigation were intermittent gross hematuria (18 of 75 examinations), regular follow-up examinations (40 of 75), incidental findings (5 of 75), and other causes, such as irritative symptoms, history of endometriosis, suprapubic pain, and recurrent urinary tract infection in the remaining examinations (12 of 75).

There was no statistically significant difference in mean ages between persons in whom CC demonstrated presence and absence of bladder tumor (tumor 69.3 ± 10.5 years; no tumor 64.2 ± 11.9 years, $P = 0.057$). The proportion of women and men was also not different statistically ($P = 0.322$, chi-square test). CC demonstrated bladder tumors in 41 of 75 examinations performed. US detected 26/41 bladder tumors, and VC demonstrated 39/41 bladder tumors.

Transitional bladder cancer was present in 75.6% of patients, chronic cystitis in 9.75%, endometriosis in 4.9%, and other conditions accounted for 9.75%. Thirty-one tumors were polypoid and nine were nonpolypoid. One lesion was a vesical calculus; 61% were larger than 1 cm and 39% were $\leq$ 1cm. In 31 CCs, there was a single tumor, while in 10 CCs, multiple tumors were observed.

Tumors involved the bladder dome in 26.8% of patients, the anterior wall in 29.2%, the right lateral wall in 41.4%, the left lateral wall in 36.5%, the posterior wall in 48.7%, the trigone in 29.2%, and the bladder neck in 7.3%. No tumor was found in the ureteral orifices. Low-grade tumors accounted for 34.3% of all tumors, and high-grade tumors accounted for the remaining 65.7%.

Both US and VC had specificity of 91.2%, but sensitivity was better for VC (95.1%, with a 95% confidence interval [CI] 0.83–0.98) than for US (63.4%, with 95% CI 0.48–0.76). A statistically significant difference for NLR was also observed: US 40.1% (with 95% CI 0.26–0.60) *v*5.4% for VC (with 95% CI 0.01–0.20). There was no difference in PLR for US and VC.

Three false-positive results were observed for VC: One case of extrinsic bladder compression by an abdominal implant of endometriosis, one case of pubic symphysis osteoarthritis, and one case of multiple lesions visualized at VC but not confirmed on CC. Two false-negative results were observed for VC: a carcinoma *in situ* (CIS) lesion and a 2-mm lesion inside a bladder diverticulum that was not visualized. For US, 3 false-positive cases were observed (an abdominal implant of endometriosis, multiple lesions not confirmed on CC, and an artifact) and 15 false-negative results were identified (in 8 cases, tumors $\leq$ 1 cm, and in 7 examinations, tumors larger than 1 cm).

With regard to location (bladder site) for false-negative results, for VC this variable was not important for tumor detection. On the contrary, for US, lesions located on the anterior bladder wall and posterior bladder wall were more frequently missed. Of the 15 false-negative results, in 6 patients, the tumor was located on the anterior wall (40% of all missed tumors), in 4 patients on the posterior wall (26.7%), and in the remaining 5 patients, in other locations (33.3%).

For tumors <1 cm, VC sensitivity was 93.5 % (CI 71.6–98.8%) and US sensitivity was 50% (28%–72%); For tumors larger than 1 cm, VC showed 100% sensitivity (85%–100%), and US had a sensitivity of 73.9% (53.5%–87.4%). For tumors <1 cm, VC showed a better tendency to detect lesions than US ($P = 0.06$). For tumors larger than 1 cm, no statistically significant differences were found when comparing US with VC.

Multiple tumors had a better detection rate by both methods ($P < 0.001$). For patients with multiple tumors, every lesion was correctly identified by VC (specificity =100%), and US had 80% sensitivity. Histologic grade was positively correlated to detection rate for US ($P < 0.01$), but not for VC.

VC had better accuracy in the detection of polypoid tumors compared with US ($P < 0.05$). For sessile lesions, no statistically significant difference between the imaging methods was demonstrated.

No complications for US, VC, and CC were observed in our study.

Discussion

Although CC remains the gold standard for bladder tumor evaluation because of the ability to obtain tissue for histologic evaluation and because flexible cystoscopy can be

carried out under local anesthesia on an outpatient basis, an interesting study demonstrated patients' preference for less invasive methods of diagnosis and surveillance.[11] In this study, patients favored the combination of transabdominal and transrectal US over flexible cystoscopy and rigid cystoscopy. They considered the combined US much more comfortable than CC.[11]

Moreover, CC is invasive, time-consuming, and expensive. Sedation is frequently necessary, and iatrogenic injury to the urethra and bladder may occur. Urinary sepsis develops in 5% to 10% of patients. In addition, certain areas of the bladder mucosa are recognized as potential blind spots for CC. Because of the limited flexibility of both rigid and fiber optic cystoscopes, the mucosa of the bladder neck is difficult to visualize. Prominent bladder trabeculation can obscure a small lesion in a diverticulum, and marked prostatic hypertrophy or severe urethral stricture may impair CC. These patients, therefore, could be more suitable for imaging methods such as VC.[1–9] In this setting, VC, with its convenience, might have a great role in children and in adults who cannot tolerate cystoscopy.

Different imaging techniques are available for bladder tumor detection. US is the most used method in daily practice. It is a noninvasive, rapid, and inexpensive radiologic examination. Estimated costs, including technical and professional fees, range from $150 to $300 for transabdominal US, compared with $300 to $400 for VC and $450 to $600 for CC. It has several drawbacks, however, such as low sensitivity, and is an operator-dependent examination.

Sensitivity of transabdominal US for bladder tumors varies from 26% to more than 80% in the literature.[11–15] Most studies show that transabdominal bladder US is especially poor in detection of tumors smaller than 5 mm.[12] Another important point is bladder tumor site influences on the US detection rate.[16] Anterior wall tumors have a lower detection rate because of reverberation artifacts.

VC has been recently applied to study bladder tumors. It consists of 3-D computer-rendering techniques with the possibility of interactive intraluminal navigation through the bladder. VC is a low-invasive examination (all that is needed is a urethral catheter to insufflate room air), is more comfortable for the patient, and has a very low rate of complications. It can also depict extravesical anatomy, which is important for staging.[1–9]

A major limitation of VC compared with CC is the inability to depict subtle alterations, such as CIS, and to provide tissue for histologic evaluation.[5] Difficulty in visualizing small lesions (<4 mm) was also reported.[5] Another limitation of VC would be radiation exposure. In our study, we adopted "low-dose CT," with about 40% of the radiation dose used in a regular abdominal CT. We chose his first because of the high contrast between the bladder wall and its air-content, which offers accurate information without needing high levels of kV and mAs. In addition, the scanned area, which is limited to the bladder, also reduces radiation exposure. In our experience, we believe VC performed with CT is easier, faster, cheaper, and more sensitive than MRI to detect small bladder lesions.

The objective of our study was to compare transabdominal US and VC for bladder tumor detection and to analyze how bladder tumors variables, such as size, number, grade, site, and type influence detection by these imaging methods. In our study, only one experienced person performed and interpreted the US and CT images, which is a limitation of our study. We believe, however, that experienced radiologists would have similar performances in interpreting examination results.

Overall, VC was shown to be more sensitive in the detection of bladder lesions than US. US had a considerable number of false-negative examinations that were affected mainly by size and site; therefore, it is less reliable if negative (Fig. 1A). Specificity was the same for both examinations, which showed a small number of false-positive examinations. Consequently, in clinical practice, if a patient has a VC or US with a lesion, it is very likely that the patient have a bladder tumor.

Compared with other studies,[1–9] we had very good figures for VC. We found that performing VC with patients in the supine and prone positions after draining residual bladder urine, performing axial images and 3-D reconstruction of bladder walls, and also creating a 3-D air-content image of the bladder (Figs. 1B, 1C) helped to avoid missing tumors.

VC after axial review facilitated interpretation in difficult cases (such as in the case depicted in Figs. 1A, 1B, and 1C) and prevented false-negative results in the other 5% (2/41 tumors). Moreover, two-dimensional (2-D) US, compared with VC, had limited value in detection of bladder lesions, especially when lesions were small and located on anterior and posterior walls. Polypoid tumors were depicted better by VC.

Recently, 3-D US has been introduced for hematuria evaluation and compared with 2-D US, with better diagnostic features using 3-D US. 3-D US gave a correct diagnosis in 86% of cases in hematuria evaluation.[17] It would be interesting to compare 3-D US with VC. In addition, the variables in our study (type, grade, multiplicity, and especially size and site) should be assessed for 3-D US to see if small lesions and tumors located on anterior and posterior walls could be revealed with more precision.

Regarding the number of lesions, as was expected, we observed that multiplicity enhances the chances of detection by both methods. In terms of size, we demonstrated that for tumors >1 cm, no statistically significant difference between US and VC existed, and for small tumors (≤1 cm), VC showed a better tendency to detect lesions than US ($P = 0.06$).

High-grade tumors had a better detection rate on US than low-grade lesions. Grade did not interfere with VC detection, but in our study and according to the literature,[5] VC missed CIS lesions. In selected patients, it would be useful to associate FISH (fluorescence *in situ* hybridization) with VC in the follow-up of high-grade lesions or CIS to enhance detection accuracy, provided that the sensitivity of FISH was shown to be 100% for CIS and 94% for high-grade lesions.[18]

Further research should compare imaging methods for bladder tumors. This would help to spare cystoscopy in the follow-up of patients with bladder tumors, especially superficial bladder cancer, a disease associated with a high recurrence rate. After an initial mandatory cystoscopy to provide a histologic diagnosis, patients might be monitored according to disclosed tumor variables (such as size, site, grade, and staging). Different follow-up protocols seem to be more rational than a standard follow-up protocol for every bladder cancer patient. In addition, imaging might

have a great role in children and adults who cannot tolerate cystoscopy.

VC showed good sensitivity and specificity and might be a useful tool for diagnosis and surveillance of bladder tumors. All imaging methods for bladder neoplasm detection, however, are still in development and have a way to go before they supplant cystoscopy.

Conclusions

VC showed better accuracy in the detection of bladder neoplasms, especially in tumors smaller than 1 cm in diameter and for polypoid lesions, when compared with transabdominal US. For VC, bladder tumor detection did not seem to be affected by the bladder site involved nor the tumor grade, while for US, tumor site and grade appeared to affect detection. Consequently, US had a low sensitivity, considering all the studied variables.

Virtual cystoscopy is a promising method in diagnosis and follow-up of bladder tumors and might help the urologist to reduce the number of cystoscopies for bladder tumor surveillance.

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Abbreviations Used

CC = conventional cystoscopy
CI = confidence interval
CIS = carcinoma *in situ*
CT = computed tomography
ICDO = International Classification of Diseases for Oncology
MRI = magnetic resonance imaging
NLR = negative likelihood ratio
PLR = positive likelihood ratio
3-D = three-dimensional
2-D = two-dimensional
US = ultrasonography
VC = virtual cystoscopy