Correlation of Transabdominal Ultrasonography and Cystoscopy in Follow-up of Patients with Non-muscle Invasive Bladder Cancer

Ahluwalia Puneet¹ · Nair Balagopal² · Kumar Ginil² · Mathew Georgie² · K. V. Sanjeevan² · Thomas Appu²

Received: 5 August 2016 / Accepted: 11 July 2017 / Published online: 21 July 2017
© Indian Association of Surgical Oncology 2017

Abstract Cystoscopy (CS) is considered to be the gold standard in the follow-up of non-muscle invasive bladder cancer. However, CS is invasive, time-consuming, and expensive. On the other hand, modern sensitive transducers have improved the imaging of urinary tract rendering transabdominal ultrasonography (US) more effective in visualizing intraluminal filling defects in the bladder than it was in the past. Twenty-five follow-up patients of low-risk bladder cancer meeting the inclusion and exclusion criteria were included in study. Ultrasonography of the bladder was performed by a single senior radiologist, and subsequently, these patients were subjected to flexible cystoscopy under local anesthesia. Pain score was calculated for each of the cystoscopies done. Findings of

transabdominal ultrasound of the bladder were correlated and compared with those of cystoscopy. Subjects with US and/or CS findings suggestive of recurrence underwent transurethral resection of bladder tumor (TURBT) under general anesthesia and confirmation of the bladder carcinoma was achieved by the histopathological examination. Mean patient age was 60.56 years with range of 29 to 77 years. The sensitivity of modern ultrasonographic techniques was found to be 84.61% with specificity of 91.7% taking flexible cystoscopy as the gold standard for detection of recurrence. The accuracy of US was 88% with positive predictive value of 91.7% and negative predictive value of 84.61%. Technological evolution has improved the accuracy of ultrasonography in diagnosis of bladder carcinoma. It represents a valuable surveillance tool in selected sub group of low risk non-muscle invasive bladder cancer patients.

✉ Ahluwalia Puneet
puneet1923@gmail.com

Nair Balagopal
balagopalnair@aims.amrita.edu

Kumar Ginil
drginil@gmail.com

Mathew Georgie
georgiemathew@aims.amrita.edu

K. V. Sanjeevan
sanjeevankv@aims.amrita.edu

Thomas Appu
apputhomas@aims.amrita.edu

Keywords Non-muscle invasive bladder cancer · Ultrasonography · Cystoscopy · Surveillance

Introduction

Majority of the bladder tumors are non-muscle-invasive carcinomas (NMIBC) and comprise about 60–80% of the total number. Endoscopic resection is the initial treatment for this disease. Risk of recurrence after primary treatment depends upon the risk category of tumor, various prognostic factors, patient's adherence to strict surveillance protocol, and adjuvant treatment [1, 2]. In patients with low-, intermediate-, or high-risk disease, about 20, 40, and 90%, respectively, develop tumor recurrence [3]. The recommendation for surveillance in NMIBC is based on repeat cystoscopies (CS). CS is considered to be the gold standard in the follow-up of the NMIBC recurrence because of its well-established advantages.

¹ Department of Surgical Oncology, Max Institute of Cancer Care, Max Smart Superspeciality Hospital, Press Enclave Road, Saket, New Delhi 110017, India

² Department of Urology, Amrita Institute of Medical Sciences, AIMS-Ponekkara, Kochi, Kerala 682041, India

However, CS is invasive, time-consuming, expensive, needs sedation frequently, and may cause infection as well as iatrogenic injury to the urethra and bladder [4]. On the other hand, ultrasonography (US) is a non-invasive, well-accepted, cost-effective diagnostic method and technological advancement has rendered transabdominal ultrasonography more effective in visualizing intraluminal pathology in the bladder than before [5]. Some investigators argue that CS is not always needed and suggest the systematic use of US alone or in combination with urine cytology for follow-up of NMIBC [6–8]. Moreover, the compliance of cystoscopic surveillance may also depend on access of healthcare facilities as well as the perceived need for follow-up in low-risk NMIBC particularly in lower median income group. There is still paucity of literature concerning the patient's tolerability and acceptance level of urological endoscopic procedures [9].

Almost 50% of NMIBC belong to the low-risk category with very low risk for progression and a sparse recurrence rate with the recurrence being of the same stage and grade as the primary tumor in vast majority. Therefore, aggressive surveillance may not be necessary and certainly can be bothersome [10, 11]. US constitutes a simple and quick examination which is not associated with any complication inherent to CS and can be safely performed on all individuals with no restrictions. In the past, various authors have proposed the use of non-invasive imaging tests in the initial investigation for detection of bladder carcinomas [12, 13]. However, due to the lower accuracy of the older devices, US has been accused of not being an appropriate method for the follow-up of bladder cancer [14]. Current scanners that combine several different transducers and color or spectral Doppler imaging facilities are more accurate in the visualization of intraluminal filling defects of the bladder than they were before [15]. 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 with plaque-like lesions being certainly harder to detect than polypoid ones [16]. Nevertheless, US may prove to be a cheap and effective alternate follow-up tool in selected patients with non-muscle invasive bladder cancer. The present study was conducted to determine the accuracy of ultrasonography as a surveillance tool in low-risk NMIBC.

Material and Methods

This prospective study was conducted from November 2011 to July 2014. Based on the available information on the sensitivity of ultrasonography with respect to cystoscopic findings in follow-up of patients with NMIBC following transurethral resection of bladder tumor (TURBT) and with 95%

confidence and 20% allowable error, minimum sample size was computed as 25.

The primary objective was to study the accuracy of transabdominal ultrasonography of the bladder in detecting recurrent tumors in patients with non-muscle invasive transitional cell carcinoma (stage Pa, low grade) of the urinary bladder as compared to flexible cystoscopy (gold standard). The secondary objective was to compare the pain score and tolerability of flexible cystoscopy and abdominal ultrasonography.

Written informed consent was taken from all the patients. A total of 25 patients presenting to the urology department irrespective of age and sex, having undergone one or more transurethral resections (TUR) for non-muscle invasive transitional cell carcinoma (stage Pa) of the urinary bladder and meeting the inclusion and exclusion criteria were included in the study. The patients in the study had undergone last TUR/check cystoscopy at least 3 months prior to the study. Urine cytology was done as a part of follow-up to rule out any evidence of high-grade tumor or CIS.

Inclusion criterion was established diagnosis of non-muscle invasive bladder carcinoma (low grade, stage Pa) confirmed in the pathology report of previous TURBT. Exclusion criteria included patients with evidence of muscle invasion, previous diagnosis of carcinoma in situ, high-grade transitional cell carcinoma (TCC). Patients with previous urinary bladder surgery and small-capacity bladder (e.g., neurogenic bladder, post-partial cystectomy, post-ectopia vesicae repair, thimble bladder) were also excluded from the study as these conditions were suboptimal for transabdominal ultrasonography of the urinary bladder. Symptomatic patients, e.g., with hematuria or with irritative voiding symptoms, were also excluded as were patients who defaulted on follow-up protocol. Malignancies of the bladder other than transitional cell carcinoma, e.g., adenocarcinoma/lymphoma of the bladder, were also not included.

Ultrasonography of the bladder was performed in the department of radio-diagnosis by an experienced single radiologist. All the patients were examined using an ultrasonography machine with convex array (5 MHz) probe. The urinary bladder was scanned at sagittal, axial, and oblique planes with convex probes. In selected patients, 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) 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 vascular and therefore arising from the bladder wall. Color Doppler parameters (filter, gain, pulse repetition frequency) were optimized for detection of slow flow in small vessels. The main diagnostic criterion for the ultrasonographic diagnosis of non-muscle invasive bladder cancer was the presence of irregular soft tissue structures of low to intermediate

echotexture projecting into the bladder lumen from a fixed mural site. Subsequently, these patients were subjected to flexible cystoscopy using 15.5 French flexible cystourethroscope under local anesthesia in the department of urology within 1 to 3 days of ultrasonography and findings of cystoscopy regarding site, size, and number of tumor recurrences were recorded. The urologist was blinded with respect to the ultrasonography 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. Pain score was calculated for each of the cystoscopies done. Each subject was provided with a visual analogue scale for pain assessment, scaled from 0 to 10 to measure discomfort or pain level of CS (1–3 no discomfort-high tolerability, 4–7 moderate discomfort-intermediate tolerability, 8–10 excessive discomfort-low tolerability). Findings of transabdominal ultrasound of the bladder were correlated and compared with those of cystoscopy. Any papillary tumor or bladder wall irregularity was considered as positive finding in either of modality and was included as abnormal/suspicious. Subjects with US and/or CS findings suggestive of recurrence underwent TURBT under general anesthesia and confirmation of the bladder carcinoma was achieved by the histopathological examination of the submitted specimens of bladder biopsy in each case.

Statistical analysis included validity parameters such as sensitivity, specificity, P plus, P minus, and accuracy. McNemar's chi-square test with correction factor was applied to test the departure from agreement between the two tests. Statistical significance of difference in pain score between ultrasonography and flexible cystoscopy was tested using Wilcoxon's signed rank test.

Results and Observations

The age of examined subjects ranged from 29 to 77 years with a mean of 60.56 years and median of 63 years. There were 23 males and 2 females in the study group.

Correlation of US and Flexible Cystoscopy Findings

Findings of US were correlated and compared with those of flexible cystoscopy (Fig. 1). Twelve patients on US and 13 patients on flexible cystoscopy, respectively, were found to have either papillary growth or bladder wall irregularity. Eleven patients had concurrence regarding abnormal/suspicious findings in both of these modalities whereas two patients which were normal in ultrasonography were found to have positive findings on flexible cystoscopy. Similarly, one patient who had normal findings on cystoscopy was found to have positive findings on US.

According to our findings, the sensitivity of modern ultrasonographic techniques was found to be 84.61% with specificity of 91.7% taking flexible cystoscopy as gold standard for detection of recurrence. The accuracy of US was 88% with positive predictive value of 91.7% and negative predictive value of 84.61%. The *p* value was 1.00, which showed no statistical significance of difference between efficacy of both modalities (Table 1).

The median pain score in flexible cystoscopy was 4 (range of 2–6) demonstrating moderate discomfort where as it was 1 (range 1–2) on US demonstrating excellent tolerability. The *p* value was less than 0.001, which showed significant difference in tolerability of procedure.

Correlation of US and Flexible Cystoscopy Findings with Cystoscopy Under Anesthesia

Patients with findings suggestive of recurrence on US and/or CS underwent rigid cystoscopy under anesthesia using 30° telescope in the operation theater. In total, 14 patients underwent cystoscopy under anesthesia. All the 14 patients had suspicious findings (either papillary lesion or thickening/irregular bladder wall) confirmed on cystoscopy under anesthesia and underwent repeat TURBT. The specimens were sent for histopathologic examination (HPE). When correlated with findings on rigid cystoscopy under anesthesia, US had sensitivity of 85.7% whereas sensitivity for flexible cystoscopy was 92.86% (Table 2).

On histopathology, 12 out of 14 submitted specimens had evidence of low-grade TCC/PUNLMP (papillary urothelial neoplasm of low malignant potential) on HPE. Two patients had non-malignant biopsy. In all 14 patients who underwent repeat TURBT, final HPE findings were further correlated with their respective findings on initial US and flexible cystoscopy (Table 3).

Correlation of US and Flexible Cystoscopy Findings with Final HPE

Out of 12 proven cases of recurrence on HPE, US had suspicious or abnormal findings in 10 cases whereas 2 confirmed recurrences on HPE were missed by US. Furthermore, both the cases predicted to be suspicious of recurrence on US were negative on final histopathology. Flexible cystoscopy predicted recurrence in all 12 proven cases on HPE. One patient, who had erythematous lesion with irregular bladder mucosa on flexible and rigid cystoscopy, was found to have no evidence of malignancy on final HPE. Furthermore, another patient, who had irregular posterior wall on US, had normal findings on flexible cystoscopy. This patient was posted for cystoscopy under anesthesia as patient had moderate discomfort during flexible cystoscopy under local anesthesia. Rigid cystoscopy under anesthesia was suggestive of irregular posterior wall

Fig. 1 Transabdominal ultrasound and subsequent flexible cystoscopy showing papillary recurrence in posterolateral wall of a 62-year-old female

bladder mucosa and TURBT was done. However, the final HPE was not malignant in this case.

Accuracy of US According to Size and Site of Recurrence

The sensitivity of US was also evaluated according to the site and size of recurrences. Ultrasound was more accurate in detection of tumor recurrences in lateral wall and trigone whereas its accuracy is less for recurrences in the dome and anterior wall. The present study had one patient with recurrence on anterior wall, which was missed by US. Out of two recurrences on the dome, US missed one recurrence. Also, recurrences less than or equal to 5 mm were difficult to detect as compared to larger tumors (Table 4).

Discussion

Attempts to modify the standard approaches to surveillance for patients with non-muscle invasive disease have been 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 CSs who are at low risk of recurrence and progression. If the initial CS is negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years. In contrast, patients with tumors at high risk of progression should have a cystoscopy every 3 months. If negative, the following CSs should be repeated every 3 months for a period of 2 years,

semiannually 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.

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 [17]. There is a paucity of prospective data examining alternative follow-up methods. Few studies have indicated that suprapubic ultrasonography of the bladder was able to detect tumors as small as 2 mm in diameter [18]. Some investigators have advocated a definitive role of ultrasonography in follow-up of patients with non-muscle invasive bladder tumors [19]. Abdominal ultrasound can be readily employed in the outpatient setting, preferably by the urologist himself to detect recurrence in these patients.

Accurate detection of bladder tumor on US 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 [20]. Despite the abovementioned pitfalls, since a skilled operator easily overcomes such difficulties, US still remains a useful diagnostic tool as it can greatly decrease the frequency of repeat cystoscopy for the follow-up of patients with non-muscle invasive bladder carcinoma treated with TURBT [19, 21].

On the other hand, CS is not always a well-tolerated procedure [10]. Actually, the idea of having a CS may make a

Table 1 Correlation of US and flexible cystoscopy findings

US	Flexible cystoscopy		<i>p</i> value
	Papillary lesion/irregular wall (<i>n</i> = 13)	Normal (<i>n</i> = 12)	
Papillary lesion/irregular wall (<i>n</i> = 12)	11 (84.6%)	1 (8.3%)	1.00
Normal (<i>n</i> = 13)	2 (15.4%)	11 (91.7%)	

Table 2 Correlation of US and flexible cystoscopy findings with cystoscopy under anesthesia

	Cystoscopy under anesthesia positive (<i>n</i> = 14)
US positive	12 (85.71%)
Flexible cystoscopy positive	13 (92.86%)

Table 3 Correlation of US findings and flexible cystoscopy with HPE findings

	HPE (<i>n</i> = 14)		<i>p</i> value
	Recurrence	Normal	
US findings			
Papillary tumor/bladder wall irregularity	10 (83.3%)	2 (100%)	1.00
Normal	2 (16.7%)	0 (0%)	
Flexible cystoscopy			
Papillary tumor/bladder wall abnormality	12 (100%)	1 (50%)	1.00
Normal	0 (0%)	1 (50%)	

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.

In a study based on Surveillance, Epidemiology, and End Results (SEER) Program–Medicare-linked database, the actual practice of surveillance for patients with non-muscle invasive bladder cancer differed substantially from the standards recommended in clinical guidelines with only 40% of the entire cohort having an examination according to recommended schedule. Patient characteristics that were independently associated with low-intensity surveillance included age 75 years or older, nonwhite, having favorable tumor histology, and high comorbidity. Residence in an urban area or in a census tract with low median income was also associated with low-intensity surveillance [22].

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 CSs 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 [23].

Although most low- and intermediate-risk non-muscle invasive bladder cancers are less likely to harm the patient if left undiagnosed and untreated, according to our belief, it may be 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. Moreover, ultrasonography remains the subjective tool for the assessment of bladder tumors especially in terms of tumor size [24]. The reported sensitivity of US is suboptimal in the diagnosis of bladder tumor of less than 5 mm [10]. However, the compliance of cystoscopic surveillance depends upon access to healthcare facilities and economic status, as well as the perceived need for follow-up in low-risk NMIBC. Based on our findings, we suggest that the follow-up schedule of patients with low-risk non-muscle invasive bladder carcinoma should include US more often which may be beneficial in terms of compliance and cost effectiveness. Patients diagnosed to be suffering from bladder carcinoma recurrence by ultrasonography should be scheduled directly and promptly for cystoscopy and bladder tumor resection.

Conclusion

Technological evolution has rendered ultrasonography more accurate in the diagnosis of bladder carcinoma. While CS (and biopsy) remains the gold standard, ultrasonography represents a valuable tool in the initial radiological investigation for detection of bladder carcinomas recurrence. Ultrasonography can be considered as a surveillance modality in selected low-risk non-muscle invasive bladder cancer patients who are likely to be noncompliant with surveillance cystoscopy as poor access to health care facilities and low socio-economic strata.

Compliance with Ethical Standards

Sources of Support Nil.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Yamada T, Tsuchiya T, Kamei S (2006) Analysis of factors affecting recurrence and prognosis of superficial bladder cancer-study of 800 patients. *Nippon Hinyokika Gakkai Zasshi* 97:33–41
2. Falke J, Witjes JA (2011) Contemporary management of low-risk bladder cancer. *Nat Rev Urol* 8:42–49
3. Shelley MD, Mason MD, Kynaston H (2010) Intravesical therapy for superficial bladder cancer: a systematic review of randomized trials and meta-analyses. *Cancer Treat Rev* 36:195–205

Table 4 Accuracy of US according to site and size of recurrence

	Number of recurrence	Recurrence detected by US
Site of recurrence		
Right lateral wall	3	3
Left lateral wall	3	3
Anterior wall	1	0
Posterior wall	2	2
Dome	2	1
Base/trigone	1	1
Size of recurrence		
≤5 mm	5	3
>5 mm	7	7

4. Fenlon H, Bell T, Ahari H, Hussain S (1997) Virtual cystoscopy. Early clinical experience. *Radiology* 250:272–274
5. Abu-Yousef MM, Narayan AS, Franken EA, Brown RC (1984) Urinary bladder tumors studied by cystosonography. Part I: Detection *Radiology* 153:223–226
6. Viswanath S, Zellhof B, Ho E, Sethia K, Mills R (2008) Is routine urine cytology useful in the haematuria clinic? *Ann R Coll Surg Engl* 9:153–155
7. Pegoraro C, Bondavalli C, Molani L (1997) Suprapubic bladder ultrasonography and urinary cytology: indications and limits in the follow-up of superficial bladder tumors. *Arch Ital Urol Nefrol Androl* 63:127–129
8. Vera-Donoso CD, Llopis B, Oliver F, Server G, Alonso M, Jimenez-Cruz JF (1990) Follow-up of superficial bladder cancer: how to spare cystoscopies? *Eur Urol* 17:17–19
9. Almallah YZ, Rennie CD, Stone J, Lancashire MJR (2000) Urinary tract infection and patient satisfaction after flexible cystoscopy and urodynamic evaluation. *Urology* 56:37–39
10. Konstantinos S, Hippocrates M, Marina P, Georgios P, Skolarikos A (2011) Accuracy of modern ultrasonographic techniques in the follow up of patients with superficial bladder carcinoma. *Medical Ultrasonography* 13:114–119
11. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J (2008) EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. *Eur Urol* 54:303–314
12. Gossel C, Knispel HH, Miller K, Klan R (1997) Is routine excretory urography necessary at first diagnosis of bladder carcinoma? *J Urol* 157:480–481
13. Herranz-Amo F, Diez-Cordero JM, Verdu-Tartajo F, Bueno-Chomon G, Leal-Hernandez F, Bielsa-Carrillo A (1999) Need for intravenous urography in patients with primary transitional carcinoma of the bladder? *Eur Urol* 36:221–224
14. Malone PR, Weston-Underwood J, Aron PM, Wilkinson KW, Joseph AE, Riddle PR (1986) The use of transabdominal ultrasound in the detection of early bladder tumors. *Br J Urol* 58: 520–522
15. Ozden E, Turgut AT, Turkolmez K, Resorlu B, Safak M (2007) Effect of bladder carcinoma location on detection rates by ultrasonography and computed tomography. *Urology* 69:889–892
16. Itzhak Y, Singer D, Fischelovitch Y (1981) Ultrasonographic assessment of bladder tumors. I Tumor detection *J Urol* 26:31–33
17. Mariappan P, Smith G (2005) A surveillance schedule for G1Ta bladder cancer allowing efficient use of check cystoscopy and safe discharge at 5 years based on 25-year prospective database. *J Urol* 173:1008–1011
18. Cronan JJ, Simenoe JF, Pfister RC, Newhouse JH, Ferrucci JT Jr (1982) Cystosonography in the detection of bladder tumours: a prospective and retrospective study. *J Ultrasound Med* 1:237–241
19. Vallancien G, Veillon B, Charton M, Brisse JM (1986) Can transabdominal ultrasonography of the bladder replace cystoscopy in the follow up of superficial bladder tumours. *J Urol* 136:32–34
20. Rousseau MC, Straif K, Siemiatycki J (2005) IARC carcinogen update. *Environ Health Perspect* 113:A580–A581
21. Boccon-Gibod I, Le Portz B, Godefroy D, Steg A (1985) Suprapubic ultrasonographic in follow up of superficial bladder tumours. *Eur Urol* 11:317–319
22. Deborah S, Lillian JH, Farhang R, Peter BB, Harry H, Colin BB (2003) Adherence to surveillance among patients with superficial bladder cancer. *J Natl Cancer Inst* 95:588–597
23. Raitanen MP, Leppilahti M, Tuhkanen K, Forssell T, Nylund P, Tammela T et al (2001) Routine follow-up cystoscopy in detection of recurrence in patients being monitored for bladder cancer. *Ann Chir Gynaecol* 90:261–265
24. Racioppi MA, Cappa EM, D'Agostino DA, Filianoti AL, Pugliese DA, Cadeddu CH et al (2013) Size of bladder cancers: correlation among different types of measurement. *Urol Int* 90:191–194