Imaging in gynecological disease: clinical and ultrasound characteristics of urinary bladder malignancies

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ABSTRACT:

Objectives. To describe clinical and ultrasound characteristics of urinary bladder malignancies diagnosed on transvaginal ultrasound in women presenting with suspected gynecological problems.

Methods. This is a multicenter retrospective study of women with histological diagnosis of urinary bladder malignancy that was suspected on transvaginal ultrasound examination. The cases were collected from three centers which specialize in the use of pelvic ultrasound between January 2007 and October 2018. Clinical data were obtained from the computer databases and all tumor images were assessed by two authors (DJ and JK) to look for characteristic sonographic patterns. We have compared the characteristics of tumors seen in women presenting with symptoms suspicious of urinary bladder malignancy and those without such symptoms.

Results. Thirty women with a confirmed diagnosis of urinary bladder malignancy on histological examination were included. Median age at diagnosis was 70.5 years (range 36-88). The most common presenting symptom was postmenopausal bleeding which was recorded in 18 women (60%). Ten women (33%) had symptoms suspicious of bladder malignancy: six had unexplained visible hematuria, three had unexplained recurrent urinary tract infections and one woman had dysuria and microhematuria. On histological examination 23 women (77%) were diagnosed with primary bladder malignancy whilst seven women (23%) had metastases in the bladder from other primary tumors. Out of 23 primary tumors, 21 (91%) were of urothelial origin (12 low-grade and 9 high-grade). Most low-grade urothelial carcinomas appeared on ultrasound as irregular papillary growth (11/12, 92%) and they were moderately to highly vascular on color Doppler examination (8/12, 67%). The ultrasound

appearances of primary non-urothelial and metastatic tumors varied without a clear common morphological tumor pattern. The tumors found in women with symptoms suggestive of bladder malignancy did not differ unequivocally from those detected in other women in their size, ultrasound morphology, vascularity or histological type.

Conclusion. Urinary bladder malignancies can be detected in patients undergoing transvaginal ultrasound examination for suspected gynecological problems. Primary urothelial cancers have relatively uniform morphological pattern, whilst the appearances of other bladder malignancies are more variable.

AIM

To describe clinical and ultrasound characteristics of urinary bladder malignancies diagnosed on transvaginal ultrasound in women presenting with suspected gynecological problems.

BACKGROUND

Epidemiology

There are 10,300 new patients diagnosed with malignant tumors of the urinary bladder in the UK every year, which ranks it as the 10th most common malignant disease in the general population. The incidence in women is 5.1-5.8 per 100,000/year in the UK, where it represents 2% of all diagnosed malignancies in women[1, 2]. The median age at diagnosis in women is 71 years[3]. It is estimated that 45% of all bladder malignancy cases are caused by smoking, whilst 5-6% of cases are related to workplace exposures[2, 4]. Women with recurrent or chronic bladder infections and those who have an ongoing source of bladder inflammation have an increased risk of developing malignant tumors of the urinary bladder. Other known risk factors include older age and genetic predisposition[4, 5].

Microscopy

The bladder wall consists of four anatomic layers: the lumen is lined by the transitional epithelium or urothelium, which is made of three to seven layers of stratified flat cells. These cells can change shape as the bladder distends. The vascular lamina propria represents the second layer underneath the epithelium. The third layer is deep to the lamina propria and consists of bundles of smooth detrusor muscle (muscularis propria). Connective tissue forms the fourth adventitial layer[6].

Primary malignant urinary bladder neoplasms most commonly arise from the epithelium, but in rare cases they can also develop from any of the other layers of the bladder wall. Classification of tumors is based on histopathological criteria and they are broadly classified as either epithelial or non-epithelial (mesenchymal), with over 95% being epithelial[6]. Epithelial tumors with differentiation towards normal urothelium are defined as urothelial neoplasms and they account for 90% of all bladder malignancies[5]. The 2004 World Health Organization (WHO) grading system categorizes urothelial carcinoma as low or high grade on the basis of architectural abnormalities and cytological atypia[7]. Although pure urothelial carcinoma accounts for most bladder malignancies, it frequently undergoes different pathways of differentiation, resulting in a wide range of histological variants. Urothelial cancer with squamous differentiation is by far the most common variant. Focal areas of squamous differentiation are reported in 20-40% of urothelial carcinomas and are usually associated with an advanced stage[8]. This variant is typically characterized by the presence of intercellular bridges or keratinization. Urothelial cancer with glandular differentiation is another common type, present in about 6% of cases of bladder malignancies[9]. Although squamous or glandular differentiation can be widespread in bladder urothelial carcinoma, the terms “squamous cell carcinoma” and “adenocarcinoma” are reserved for carcinomas of pure squamous or glandular differentiation, with no element of urothelial carcinoma.

Urothelial carcinoma in situ is a lesion limited to the epithelial lining[10]. Invasive urothelial carcinomas are defined as tumors which infiltrate the basal membrane. Depending on the depth of infiltration at diagnosis, urothelial bladder tumors are classified either as non-muscle-invasive (carcinoma in situ, Ta or T1 according to tumor-node-metastasis, TNM, system) or muscle-invasive carcinomas[11]. "Superficial" bladder tumors include those limited to the mucosa (stage Ta) and those infiltrating the submucosa but not beyond (stage T1). Tumors invading the muscularis propria and beyond (T2 to T4) are considered advanced disease[11].

Primary squamous cell carcinoma accounts for less than 5% of urinary bladder malignancies[12]. These tumors are usually high grade and more locally aggressive than urothelial carcinomas[13]. Adenocarcinoma of the bladder is a rare histologic type of bladder cancer, which accounts for less than 2% of cases[14]. Very rare epithelial tumors are neuroendocrine carcinoma and carcinoid, melanoma of the urinary bladder and Müllerian type tumour[15, 16, 17].Metastatic adenocarcinoma in the bladder is more common than primary adenocarcinoma. The bladder can be invaded either by direct extension or by metastasis from a distant site via hematogenous or lymphatic spread. Large bowel, cervix and endometrium are the most common primary sites[18]Mesenchymal cells represent another potential source of bladder neoplasm, differentiating to muscle, nerve, cartilage, fat, fibrous tissue, and blood vessels. These neoplasms arise from the submucosal portion of the bladder wall. Resulting malignant tumors include rhabdomyosarcoma, leiomyosarcoma, lymphoma, and osteosarcoma, which account for a minimal percentage of bladder malignancies[19]. Bladder leiomyosarcoma represents the most common primary malignant mesenchymal tumor of the bladder and is typically organized in clusters of spindle cells[19]. According to the level of cellular atypia, it is classified as well-differentiated, moderately differentiated and poorly differentiated,

each one with an increasing mitotic activity[20]. Necrosis, cystic degeneration and hemorrhagic areas may be found within high-grade leyomiosarcoma[19].

Macroscopy

Urinary bladder malignancies display a range of morphological features including papillary, polypoid, nodular or diffuse pattern of growth[21]. They may be solitary or develop as multifocal lesions. The vast majority of newly diagnosed patients present with non-muscle-invasive disease[5].

Low grade urothelial carcinomas are predominantly papillary and exophytic in appearance, consisting of papillae containing well-defined fibrovascular cores[22]. There is a great variety in the size of the lesions. High grade urothelial carcinomas are more variable in appearance; however the majority tend to present as solitary lesions[23]. High grade urothelial carcinomas are usually friable and have a high propensity to bleed[23].

Non-epithelial malignancies are extremely rare and descriptions of their morphology are sparse[20] They tend to manifest morphological features similar to their counterparts in the soft tissues, with an invasive growth pattern which typically involves all layers of the bladder[20]. These neoplasms present grossly as irregular, firm and infiltrative nodules whose size ranges from 5 to 10 cm[19].

Clinical symptoms and prognosis

Although urinary bladder malignancies are more common in men than in women, survival rates tend to be worse for women. The 5-year overall survival for all stages combined is 84% for men and 75% for women[24]. A possible explanation is that bladder malignancies are diagnosed later in the course of the disease in women than in men. In the absence of an effective screening tool, bladder malignancies are usually diagnosed in symptomatic patients with visible hematuria being the most common presenting symptom[5]. Urinary bladder malignancies may present with non-specific symptoms such as dysuria, urinary frequency and urgency which are usually associated with urinary tract infections. Studies have shown that women reporting such symptoms are more likely to be treated empirically than men, which can cause a delay in detecting these tumours[25, 26].

Transurethral resection of the bladder tumor is the gold standard to confirm the diagnosis and investigate the extent of disease spread within the bladder. This procedure also allows for complete excision of the visible tumor in early cases. Histological staging is by the TNM staging system, in which the tumor (T) value is based on the depth of invasion into the bladder wall[11]. At presentation, around 75% of all patients (men and women) have non-muscle invasive bladder cancer (≤T1) and 25% have muscle-invasive or metastatic disease (≥T2)[5]. Although tumor grade is the most relevant prognostic factor in non-muscle-invasive bladder cancer, the stage is by far more important in advanced disease[5].

Histology, grade and depth of invasion are helpful to assess the probability of recurrence or progression to a more advanced stage and are therefore used to stratify patients into risk groups[27]. Transurethral resection of the bladder tumor is the first-line treatment in low risk patients presenting with suspected bladder malignancy, whereas high risk patients are offered cystectomy[4]. After surgical resection, low-risk patients are usually offered intravesical

treatment, which includes immunotherapy and chemotherapy. It helps reducing the risk of recurrence and progression of disease[4]. The most commonly used agents for intravesical chemotherapy are mytomicin C, gemcitabine and Bacillus Calmette-Guerin (BCG). However, there is no standard regimen and patients are usually referred to expert oncology centers for these treatments[28].

Urothelial bladder cancers can recur in the same or another part of the bladder. The percentage of patients with non-muscle invasive disease experiencing a recurrence or a new occurrence of bladder malignancy within five years ranges from 15% to 31% depending on specific risk factors, including tumor size and number of lesions, stage, grade and presence of cancer in situ[27]. In view of that, bladder malignancy should be perceived as a chronic condition which requires continuous surveillance and follow-up[29].

METHODS

We have carried out a retrospective analysis including all women in the participating ultrasound centers with a histological diagnosis of bladder malignancy that was suspected on transvaginal ultrasound examination. We included women who were seen at gynecological outpatient clinics which specialize in the use of pelvic ultrasound. All women diagnosed with bladder cancer seen between January 2007 and October 2018 were included. The following centers participated in the study: Institute for Women's Health, University College Hospital, London, UK, Department of Obstetrics and Gynaecology, University Hospitals, K.U. Leuven, Belgium and Department of Obstetrics and Gynaecology, Skåne University Hospital, Malmö Sweden. Information on age, menopausal state, presenting symptoms and risk factors (smoking, personal or family history of urinary bladder malignancy) was collected from the computer databases of the participating centers. In all women, a transvaginal scan was performed in a systematic way by highly trained operators. Women were asked to empty their bladder prior to examination, so that it was only partially filled at the time of the assessment of the urinary bladder which was performed as a part of gynecological ultrasound examination. All suspected bladder tumors were recorded and measured. The images were stored in the computer databases. All patients with suspicious bladder lesions were referred to urology clinic for further investigations and management.

The sonographic characteristics of bladder tumors were evaluated retrospectively using a uniform structured approach by two of the authors (DJ and JK). The tumors were classified either as papillary lesions (solid irregular protrusions into the bladder lumen), solid lesions (tumor with echogenicity suggestive of solid tissue but without papillary, irregular growth pattern) or plaques (areas of focal wall thickening with the base length larger than the height). The echogenicity was compared to the normal myometrium and defined as hypo-, hyper-,

isoechogenic, or as mixed when the echogenicity was not uniform. Vascularity of tumors was assessed subjectively by color Doppler using a semi-quantitative method ranging from 1 (avascular lesions) to 4 (highly vascular lesions)[30]. Participating centers were asked to provide results of tumor measurements and clinical characteristics of the patients as described in the local databases.

We have compared the sonographic characteristics of tumors seen in women presenting with symptoms suspicious of urinary bladder malignancy with those of women presenting with other symptoms. We have followed the National Institute for Health and Care Excellence (NICE) recommendations to identify women with symptoms suspicious of urinary bladder malignancy. These include unexplained visible hematuria without urinary tract infection or persistent hematuria in women aged 45 years or above. In women aged 60 years or above, these also include dysuria with non-visible hematuria or recurrent unexplained urinary tract infections[31]. We present results as median, minimum and maximum values, or as number (%).

RESULTS

We have identified 32 women diagnosed with bladder malignancy suspected on transvaginal ultrasound. One woman was excluded from the final analysis because of incomplete histology data and another woman died before planned tumor biopsy. Demographic characteristics and clinical symptoms of the 30 women included are presented in Table 1. Median age at diagnosis was 70.5 years and 28/30 (93%) of the women were postmenopausal. Post-menopausal bleeding was the most common presenting symptom. It was recorded in 18/30 (60%) women. Ten (33%) of the 30 women fulfilled the NICE guidance criteria on referral for suspicion of bladder malignancy (six had unexplained visible hematuria, three had unexplained recurrent urinary tract infections and one had dysuria with microhematuria)[31].

Primary malignant bladder tumors were diagnosed in 23/30 (77%) of the women. Twenty-one of the 23 (91%) tumors were of urothelial origin, two (9%) were non-urothelial (one carcinosarcoma and one clear-cell carcinoma). In 7/30 (23%) women the tumor was metastatic to the bladder (four ovarian adenocarcinomas, one vaginal adenocarcinoma, one cervical squamous carcinoma, and one pelvic osteosarcoma).

Sonographic features of bladder malignancies according to histological type are shown in Table 2. The most commonly diagnosed tumor was low grade urothelial carcinoma (n =12) which typically presented as an irregular papillary exophytic growth protruding into the bladder lumen (Fig. 1). In most cases [8/12 (67%)] it appeared highly or moderately vascular (Fig. 1 e-g). High grade urothelial tumors (n =9) were usually larger than low grade urothelial tumors at presentation and they were also moderately or highly vascular (Fig. 2). Similar to low grade tumors, they also typically presented with papillary growth pattern. Primary non-urothelial (Fig. 3) and metastatic (Fig. 4) tumors had varied appearance and we failed to identify a common

ultrasound pattern. One primary non-urothelial malignancy appeared as a solid tumor filling the bladder lumen (Fig. 3). One of the two primary non-urothelial malignancies and two of the seven metastatic tumors appeared as plaques in the bladder wall (Fig 4 d-f). This was different from the papillary growth of the urothelial tumors. All metastatic tumors in our series appeared with growth pattern infiltrating the bladder wall.

The sonographic characteristics of the tumors in women fulfilling NICE criteria for suspected bladder malignancy did not differ unequivocally from those of tumors in other women either in size, ultrasound morphology, vascularity or histological type (Table 3). Women with visible hematuria had larger tumors (median mean diameter 30.5 mm) than women without this symptom (median mean diameter 19.7 mm). Primary tumors that were muscle invasive were larger (median mean diameter 38.3 mm) than non-muscle invasive tumors (median mean diameter 19.2 mm). None of the five tumors with mean diameter <15 mm showed signs of muscle-invasiveness on histological examination.

DISCUSSION

Our study has shown that malignancies of the urinary bladder can be successfully diagnosed on transvaginal ultrasound scan. Urothelial tumors were the most common malignant lesions in our series which is concordant with the reports in the literature[32-39]. They tended to present as irregular papillary growths into the bladder lumen and were vascular on color Doppler examination. Primary non-urothelial tumors appeared as a solid growth or a plaque within the bladder wall, and this might be explained by them arising from the layers underneath the urothelium. The morphological appearances of secondary bladder tumors were variable reflecting their heterogeneous origin and histology. There appeared to be an association between the clinical symptoms, size of the tumor and the stage of the disease. Women with larger tumors were more likely to present with visible hematuria and larger tumors were more often invasive.

To the best of our knowledge our study is the largest to describe the ultrasound appearance of malignancies in the urinary bladder detected on transvaginal ultrasound in women with symptoms suggesting a gynecological problem. It is a limitation that our study is retrospective, and despite the relatively large sample size, the number of patients is insufficient to provide solid evidence of the typical appearance of different types of bladder malignancies. We can only state that there do seem to be differences in the ultrasound appearance between different tumor types.

Previous studies on transvaginal ultrasound diagnosis of urinary bladder cancer are summarized in Table 4[32-39]. The earliest study published more than 30 years ago, described malignant bladder lesions only as focal thickenings of the bladder wall[32]. This relatively vague description is likely to be explained by the lower resolution of ultrasound equipment available

at the time which precluded study of subtle sonographic features of bladder tumors. Hence, papillary lesions may have been difficult to differentiate from other solid focal lesions or localized thickenings of the bladder wall. Later reports describe urothelial carcinomas as either papillary or solid nodular growths in the bladder, which is broadly in agreement with our findings[33-39].

When evaluating the morphology of the bladder wall, adequately filled bladder is important. The bladder is a hollow organ and as it fills, the muscles in its wall relax so that it can expand. This facilitates detection of small bladder tumors which are more difficult to detect when the bladder is empty and the wall of the bladder appears thicker. Moreover, with an empty bladder, mucosal folds may be mistaken for tumors leading to false positive findings. Ideally, the bladder examination should be performed at the very end of the ultrasound examination when the bladder is usually partially filled.

Bladder tumors are perceived as rare incidental findings on gynecological transvaginal scan. Routine detailed bladder examination on transvaginal ultrasound could lead to an earlier diagnosis of bladder malignancy in women without symptoms suspicious of bladder malignancy. However, there is no evidence that an early incidental diagnosis of bladder malignancy would result in improved clinical outcomes and better survival rates. Most women in our series were postmenopausal and nearly two thirds of them presented with postmenopausal bleeding, which is a common indication for transvaginal ultrasound after menopause. It is likely that in some women with postmenopausal bleeding, bleeding from the urinary bladder is misinterpreted by the women as coming from the vagina. Postmenopausal bleeding is therefore an indication to scan not only the uterus and ovaries but also the urinary bladder. However, it is not known how sensitive and specific transvaginal ultrasound is for the diagnosis of bladder malignancy. Only a prospective study can answer that question.

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FIGURE LEGENDS:

Fig. 1 Ultrasound images of low-grade urothelial cancer. Most tumors showed irregular solitary papillary growth (a, b, c e, f). The tumors were typically isoechogenic (a, b), although some contained hyperechogenic foci (c). One low-grade urothelial cancer appeared as a solid tumor in the lateral aspect of the bladder adhering to the opposing bladder walls (d). Most were moderately or highly vascular on color Doppler examination (e, f, g). In large and highly vascular tumors, a characteristic pattern of vessel branching was sometimes observed (e, f). Smaller lesions tended to be less vascular than larger tumors.

Fig. 2 Ultrasound images of high-grade urothelial cancers. These tended to be larger than low-grade tumors. However, many expressed sonographic features similar to their low-grade counterparts and could not be easily distinguished from them. They usually grew as irregular papillary structures (a, b, c, d) and were mainly isoechogenic (a-c). Hyperechogenic areas were seen in some tumors (d). Larger cancers sometimes appeared as papillary growths filling the lumen of the bladder (e). Similar to low-grade urothelial cancers, most appeared moderately or highly vascular on color Doppler examination (f, g, h).

Fig. 3 Gray scale ultrasound image of a primary bladder carcinosarcoma in a woman presenting with visible hematuria and urinary frequency. The tumor measured 9 cm and filled most of the bladder lumen. The ultrasound appearance of this tumor differed from that of the urothelial carcinomas in our series. It was predominately solid with prominent hyperechogenic areas.

Fig. 4 Ultrasound images of metastatic bladder tumors. The appearances varied. The tumors in our series were seen either as an irregular solid structure arising from the bladder wall (a), a broad-based

papillary lesion of moderate vascularity (b) or as a plaque in the bladder wall (c). A squamous cell metastasis from uterine cervix appeared as a round solid tumor in the bladder wall and was poorly vascular on Doppler examination (d). Vaginal adenocarcinoma invading into the urinary bladder appeared as a highly vascular plaque in the bladder wall (e, f).

Table 1: Clinical characteristics of patients with urinary bladder malignancies according to histological type

Patient characteristics	Low grade urothelial carcinoma (n=12)	High grade urothelial carcinoma (n=9)	Other type of primary bladder malignancy (n=2)	Metastasis from other primary tumor (n=7)	All tumors (n=30)
Median age at diagnosis; years (range)	66 (36-88)	75 (38-85)	79 (69-81)	77 (42-84)	70 (36-88)
Postmenopausal n (%)	11 (92)	8 (89)	2 (100)	7 (100)	28 (93)
Symptoms					
Visible hematuria; n (%)	1 (8)	3 (33)	1 (50)	1 (14)	6 (20)
Postmenopausal bleeding; n (%)	6 (50)	7 (78)	1 (50)	4 (57)	18(60)
Urinary urgency; n (%)	0 (0)	1 (11)	0 (0)	0 (0)	1 (3)

	Urinary frequency; n (%)	2 (17)	1 (11)	1 (50)	1 (14)	5 (17)

cont.

Table 1. Continued

	Dysuria; n (%)	3 (25)	1 (11)	0 (0)	4 (57)	8 (27)
	Recurrent urinary tract infection; n (%)	1 (8)	0 (0)	0 (0)	2 (29)	3 (10)
	Pelvic pain; n (%)	2 (17)	4 (44)	1 (50)	2 (29)	9 (30)

Table 2. Ultrasound features of different histological types of urinary bladder malignancies

	Low grade urothelial carcinoma n=12	High grade urothelial carcinoma (n=9)	Other type of primary bladder malignancy (n=2)	Metastasis from other primary tumor (n=7)	All tumors (n=30)
Median largest diameter; mm (range)	21 (4-47)	39 (18-75)	79.5 (59-100)	30 (13-70)	28.5 (4-100)
Median mean diameter; mm (range)	16 (3-38)	35 (15-55)	74 (57-901)	24 (12-48)	25 (3-91)
TNM* stage (≥T2); n (%)	3 (25)	4 (44)	2 (100)	N/A	9/23 (39)
Morphology					
Papillary; n (%)	11 (92)	8 (89)	0 (00)	3 (43)	22 (73)
Solid; n (%)	1 (8)	1 (11)	1 (50)	2 (29)	5 (16.7)
Plaque (bladder wall thickening); n (%)	0 (0)	0 (0)	1 (50)	2 (29)	3 (10)

Cont.

Table 2. continued					
Echogenicity**					
Isoechogenic; n (%)	11 (92)	8 (89)	1 (50)	5 (71)	25 (83)
Mixed echogenicity; n (%)	1 (8)	1 (11)	1 (50)	2 (29)	5 (17)
Moderately or highly vascular; n (%)	8 (67)	6 (67)	1 (50)	4 (57)	19 (63)

**TNM*, tumor-node-metastasis system

**There were no hyper- or hypoechogenic tumors

Table 3: Ultrasound features of tumors seen in women according to National Institute for Health and Care Excellence (NICE) clinical criteria for suspected urinary bladder malignancy referral[31].

	No symptoms of bladder malignancy (n=20)	Suspicion of bladder malignancy according to NICE (n=10)
Median largest diameter; mm (range)	27 (4-70)	29 (4-100)
Median mean diameter; mm (range)	22.3 (4-57)	27.5 (3-90.7)
Histology		
Low grade urothelial; n (%)	9 (45)	3 (30)
High grade urothelial; n (%)	6 (30)	3 (30)
Other (non-urothelial, metastases); n (%)	5 (25)	4 (40)
Morphology		
Papillary; n (%)	16 (80)	6 (60)
Solid; n (%)	1 (5)	3 (30)
Plaque (bladder wall thickening); n (%)	3 (15)	1 (10)
Echogenicity *		
Isoechogenic; n (%)	17 (85)	8 (80)

	Mixed echogenicity	3 (15)	2 (20) cont.

Table 3. continued		
TNM** stage (≥T2); n (%) (non-primary metastatic tumors excluded)	5/16 (31)	4/7 (57)
Moderately or highly vascular; n (%)	14 (70)	5 (50)

*There were no hyper- or hypoechogenic tumors

***TNM*, tumor-node-metastasis system

Table 4: Review of published urinary bladder malignancy cases diagnosed on transvaginal ultrasound

	Study	No of cases (n)	Age range (years)	Postmenopausal state N (%)	Urinary symptoms N (%)	Postmenopausal bleeding N (%)	US appearance	Mean size (mm)	Histology
Tsyb et al., 1988[32]	Retrospective study	8	41-56	Not known	Not known	Not known	Bladder wall thickening or fragmentation	N/K	Primary urothelial carcinoma
Granberg et al., 1991[33]	Prospective study	5	54-76	5 (100)	0	5 (100)	Not known	23	Primary urothelial carcinoma
Abdel-Fattah et al. 2004[45]	Prospective study	3	62-85	3(100)	2 (67)	3 (100)	Nodular lesions (3)	15	2 primary urothelial carcinomas 1 benign inverted papilloma
Huang et al., 2005[35]	Case report	2	50-59	2/2 (100)	2/2 (100)	0	Nodular lesions (2)	31	1 primary adenosquamous bladder carcinoma 1 primary bladder adenocarcinoma
Huang et al., 2006[36]	Retrospective study	6	35-68	3/6 (50)	N/K	N/K	Flat lesions (3) Plateau-like elevation (1) Hump-like elevation (2)	Not known	Primary cervical squamous cell carcinoma invading the urinary bladder
Betsas et al., 2008[37]	Retrospective study	2	75-75	2/2 (100)	0/2 (0)	2/2 (100)	Papillary lesions (2)	30	Primary urothelial carcinoma
Yoshino et al., 2011[38]	Case report	1	52	1/1 (100)	0/1 (0)	1/1 (100)	Nodular lesion (1)	33	Primary urothelial carcinoma

Yakasai et al., 2011[39]	Retrospective study	3	N/K	3/3 (100)	0/3 (0)	3/3 (100)	N/K	N/K	Primary urothelial carcinoma