Symptoms and Diagnostic Tools for Bladder Cancer

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Abstract

The **symptoms of bladder cancer** (BC) can vary widely; sometimes only unspecific dysuria with irritative or obstructive symptoms can be present. **Painless gross hematuria** represents the most common symptom of BC. Ostial or urethral tumor obstruction might lead to impaired renal urine outflow, leading to **flank pain**. Advanced localized BC can display in **abdominal distention, pelvic pain, and even palpable masses** whereas metastases can be associated with multiple symptoms. **Urine tests** often represent the initial diagnostic marker. The ***urinary cytology*** **(UC),** in which exfoliated cells of the urothelium are extracted and microscopically examined, **promotes a high sensitivity in high grade (G3) tumors and carcinoma in situ.** UC should be utilized as an adjunct to cystoscopy, since positive UC can indicate urothelial tumors in the entire urinary tract. In order to improve sensitivity of UC, numerous different ***urinary marker tests*** were developed; however, a use for regular screening is not recommended, yet. In patients with suspected BC the ***white light cystoscopy*** **(WLC)** represents the diagnostic gold standard. The ***fluorescence cystoscopy*** **(photodynamic diagnosis (PDD))** shows diagnostic advantages compared to WLC, outlined in improved detection rates and improved recurrence free survival. ***Narrow-band imaging (NBI)*** represents another promising visualization tool. ***Computed tomography*** **urography and MRI** can help to identify tumorous lesions in both the bladder and the upper urinary tract.

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Introduction

Bladder cancer is the ninth most common cancer worldwide, while 430,000 new cases were diagnosed in 2012. Male patients have a strong predominance of these tumors; tobacco smoking is considered to be the main risk factor for the development of urothelial cancer. In general, survival from bladder cancer differs by region; while bladder cancer mortality slightly declines in high-income countries, less developed regions of the world have a much higher burden with more than 60% of all bladder cancer cases and half of all cancer deaths.

New treatment approaches as well as new technologies for an optimized diagnosis of bladder tumors have been established over the recent years. These current developments could help to reduce morbidity and also increase survival rates in the future.

Symptoms

At initial diagnosis bladder cancer (BC) patients may present with different symptoms. Many of these symptoms are even completely unspecific and resemble those of other diseases of the urinary tract. In early stages, many patients even do not describe any complaints at all. Bladder tumors tend to bleed with increasing size since angiogenesis plays an important role in tumor growth (Wallace et al. 2002).

As consequence the leading and also the most common symptom in BC patients is painless gross hematuria. In this case, patients often notice a brownish-reddish discoloration of their urine, but usually there are no symptoms of pain during urination. The presence of blood in the urine is quite often self-limiting. Some studies report about gross hematuria as a symptom in BC patients in up to 97.5% of all cases with an allover positive predictive value up to 10.3% (Fus and Gornicka 2016; Carson et al. 1979). Regarding this, male patients over 60 years present with the highest positive predictive value with 22.1%. The positive predictive value decreases considerable with patient's age in the same study (Kiragu and Cifu 2015).

Above this asymptomatic microhematuria may indicate BC or malignancies of the urinary tract too. However, asymptomatic microhematuria shows a lower sensitivity compared to gross hematuria and shows tumor of the urinary tract in up to 15% of all cases. With asymptomatic microhematuria one should even think of carcinoma in situ of the bladder (Bruyninckx et al. 2003; Massey et al. 1965).

Bladder tumor in general and particularly carcinoma in situ of the bladder might additionally come along with dysuria symptoms. These symptoms obviously do not just concern to men but simulate lower urinary tract symptoms with all its usual complaints. On the one hand, there are irritative symptoms like high micturition frequency, the sensation of incomplete voiding, nocturnal polyuria, urinary urgency, or even vesical tenesm. Irritative symptoms occur in up to 25% of all BC patients. A frequent cause could here be attendant urinary tract infection, which is described in up to 40% of all cases (Cox et al. 1969; Turner et al. 1977). Even more causes could be decreased bladder capacity, pain, or tumor necrosis with accompanying inflammation. As recently shown this might even be reflected in changes regarding patient's laboratory values like elevated CRP levels or leukocytosis (Ozcan et al. 2015; Grimm et al. 2015). On the other hand, there are obstructive symptoms like low urine flow rate with persistent storage symptoms that may be caused by bladder neck obstruction of local tumor growth.

Depending on the localization and the spread of the tumor, various complaints may occur. As already described bladder neck obstruction may lead to lower urinary tract symptoms as tumor growth close to the bladder ostium might effect ostial and ureteral obstruction. As a result, a sufficient urine flow from the renal pelvis to the bladder is no longer ensured, which could lead to flank pain.

In patients with locally advanced BC, you could find complaints of abdominal distention, pelvic pain, and even palpable mass at initial diagnosis. In patients with metastatic BC, afflictions dependent on the localization of metastases arise. For instance, pain caused by osseous

metastases or disrupted lymph drain of the lower limb could emerge caused by lymph node metastases.

In principle, however very unspecific, the presence of B symptoms can also be indicative for BC.

Diagnostic Tools

An adequate diagnosis for malignant lesions of the bladder is essential for an effective treatment of both: non-muscle-invasive (NMIBC) and muscle-invasive bladder cancer (MIBC). Since there is no sufficient marker for general screening and systemic early detection, numerous diagnostic tools are required to ensure effective diagnosis.

Urine tests ("dipsticks") often represent the initial diagnostic marker for symptomatic or asymptomatic patients. Urine test stripes detect even minor microhematuria quickly and effectively and have a high availability. Dipsticks should be completed by a light microscopy of urine samples. This allows further qualification as size and structure of erythrocytes can help to clarify origin of bleeding.

The ***urinary cytology*** **(UC)** in which exfoliated cells of the urothelium are extracted and microscopically examined shows a high diagnostic specificity for BC cells (90–100%). In G3 tumors, UC promotes a high sensitivity whereas only low sensitivity in G1 lesions is shown (Turco et al. 2011). For the detection of CIS the sensitivity rises up to 21–100% (Têtu 2009). Therefore, UC should be utilized as an adjunct to cystoscopy in high-risk tumors of the bladder, since positive UC can indicate urothelial tumors anywhere in the urinary tract. Nevertheless, negative UC does not exclude the presence of malignancy of the bladder. Accuracy of UC is limited by examiner's experience and can be impeded by local urinary infections, nephrolithiasis, and intravesical instillation therapy (Lokeshwar et al. 2005; van Rhijn et al. 2005).

In order to improve sensitivity of UC, numerous different ***urinary marker tests*** were developed. Different marker systems such as *NMP22, ImmunoCyt, BTA stat, BTA TRAK, cytokeratins, and FISH (UroVysion)* have been admitted by the US Food and Drug Administration (FDA) (Tritschler and Scharf 2007).

Protein-based marker systems: Nuclear matrix protein number 22 (NMP22) reflects the cell proliferation by quantifying mitotic activity. The marker system utilizes an immunoassay using monoclonal antibodies detecting the NMP22 (Tritschler and Scharf 2007). Bladder tumor antigen (BTA: BTA stat and BTA TRAK) detects complement factor H-related protein, which is typically elevated in bladder tumor patient's urine. Presence of hematuria and infection can also influence the results; therefore, BTA is not recommended as a regular screening procedure (Goodison et al. 2013). Cytokeratins (CK) are stromal proteins that can be found in BC patient's urine. Elevation of molecules such as CK-18, CK-20, and CYFRA 21-1 can be utilized as a urinary tumor marker.

Cellular-based marker systems: ImmunoCyt uses three monoclonal antibodies in patient's urine in order to detect urothelial cells. Whereas fluorescence in situ hybridization (FISH/UroVysion) detects cell alterations, indicating genetic instability as a sign of malignancy (Tritschler et al. 2013) (Table 1).

Although usually sensitivity for high-grade tumors in urinary marker tests was shown to be higher, specificity normally appears to be inferior

Table 1 Summary of urinary marker systems (Adapted by EAU Guidelines) (Babjuk et al. 2015)

Markers	Overall sensitivity (%)	Overall specificity (%)	Sensitivity for high-grade tumors (%)
FISH (UroVysion)	30–86	63–95	66–70
Immuncyt/uCyt+	52–100	63–79	62–92
NMP22	47–100	55–98	75–92
BTA stat	29–83	56–86	62–91
BTA TRAK	53–91	28–83	74–77
Cytokeratins	12–88	73–95	33–100

to UC. Therefore, current guidelines (AUA and EAU guidelines) do not recommend urine marker tests for screening, diagnosis, or follow-up of patients with BC (Babjuk et al. 2015). An additional utilization of FISH can be considered in the presence of uncertain UC results in order to enhance the specificity (Schlomer et al. 2010).

In patients with a suspected malignancy, the rigid or flexible ***white light cystoscopy*** **(WLC)** presents the diagnostic gold standard for NMIBC and MIBC. Sensitivity and specificity in WLC in terms of detection rate varies between 6–84% (sensitivity) and 43–98% (specificity) (Jocham et al. 2008). WLC efficiency depends strongly on the performing physician (Babjuk et al. 2015). If the presence of a BC is evident, a transurethral resection of the tumor (TURB) is mandatory. The procedure of TURB is the basis for both: histopathological diagnosis and the complete resection of the lesion. TURB should therefore be performed systematically and in individual steps (Babjuk et al. 2015). It is essential for the further treatment and patient's prognosis that detrusor muscle is included in resection in order to perform an adequate histological staging and in order to reduce risk of recurrence (Herr and Machele Donat 2008; Mariappan et al. 2010). Especially for CIS and micropapillary lesions, WCL and white light TURB show diagnostic limitations.

The ***fluorescence cystoscopy*** **(photodynamic diagnosis (PDD))** shows diagnostic advantages compared to WLC (Filbeck et al. 2002). Fluorescence cystoscopy utilizes violet light after an intravesical instillation of a photosensitizer like hexaminolevulinic acid (HAL). Data indicate that PDD has a significant higher detection rate compared to white light in terms of patients-levels (92% vs. 71%) and biopsies-levels (93% vs. 65%) (Mariappan et al. 2010; Mowatt et al. 2011; Kausch et al. 2010). The detection rate for CIS lesions is considered to be up to 40% higher using PDD (Kausch et al. 2010; O'Brien et al. 2013). Therefore, PDD in the initial TURB is highly recommended by different studies (Babjuk et al. 2015). Additionally PDD should be performed in patients with: multifocal tumors, high-grade tumors in patient's history, and suspected CIS (Babjuk et al. 2015; Onkologie 2016). Although the utilization of PDD significantly improves recurrence free survival and increases time to recurrence, there is no evidence for a reduction of progression rate for PDD in TURB (Mowatt et al. 2011; Yang 2014).

Narrow-band Imaging (NBI) represents another visualization tool in which different light spectra lead to a contrast enhancement between urothelium and BC. Data indicate that NBI improves tumor detection rate (Cauberg et al. 2010; Zheng et al. 2012). So far there is no evidence concerning a reduction of progression compared to WLC or PDD.

Imaging in Bladder Cancer

If there is clinical evidence for a BC, *abdominal ultrasound* of the bladder represents a noninvasive imaging of the bladder and can therefore help to identify intravesical lesions. Renal ultrasound can also help to identify hydronephrosis caused by obstructive tumor infiltration.

Computed tomography (CT) urography can help to identify tumorous lesions in both the bladder and the upper urinary tract. If CT urography is not available, MRT urography or intravenous urography (IVU) can be recommended. At the moment CT urography is the state-of-the-art imaging for the urinary tract. After diagnosis of high-risk lesions of the bladder, multifocal tumors, or tumors localized near the trigonum or ostia, CT urography is recommended (Onkologie 2016). If MIBC is evident, abdominal and thoracic CT scan is mandatory in order to complete staging. Bone scintigraphy or CT scan of the caput is only recommended if clinic indicates such imaging. MRT is only recommended for evaluation of soft tissue infiltration of tumor. So far PET-CT/MRT is not commonly recommended for staging or follow-up for BC.

References

Babjuk M (Chair), Böhle A, Burger M, Compérat E, Kaasinen E, Palou J, Rouprêt M, van Rhijn BWG, Shariat S, Sylvester R, Zigeuner R. EAU-Guidelines on non-muscle-invasive bladder cancer (Ta, T1 and CIS). Eur Urol. 2015;41:105–12.

Bruyninckx R, Buntinx F, Aertgeerts B, Van Casteren V. The diagnostic value of macroscopic haematuria for the diagnosis of urological cancer in general practice. Br J Gen Pract. 2003;53(486):31–5.

Carson CC 3rd, Segura JW, Greene L. Clinical importance of microhematuria. JAMA. 1979;241(2):149–50.

Cauberg EC, Kloen S, Visser M, et al. Narrow band imaging cystoscopy improves the detection of non-muscle-invasive bladder cancer. Urology. 2010;76(3):658–63.

Cox CE, Cass AS, Boyce WH. Bladder cancer: a 26-year review. J Urol. 1969;101(4):550–8.

Filbeck T, et al. Do patients profit from 5-aminolevulinic acid-induced fluorescence diagnosis in transurethral resection of bladder carcinoma? Urology. 2002;60 (6):1025–8.

Fus LP, Gornicka B. Role of angiogenesis in urothelial bladder carcinoma. Cent Eur J Urol. 2016;69 (3):258–63.

Goodison S, Rosser CJ, Urquidi V. Bladder cancer detection and monitoring: assessment of urine- and blood-based marker tests. Mol Diagn Ther. 2013;17 (2):71–84.

Grimm T, Buchner A, Schneevoigt B, et al. World J Urol. 2015:1–6. https://doi.org/10.1007/s00345-015-1680-7.

Herr HW, Machele Donat S. Quality control in transurethral resection of bladder tumours. BJU Int. 2008;102 (9):1242–6.

Jocham D, Stepp H, Photodynamic RW. Diagnosis in urology: state-of-the-art. Eur Urol. 2008;53(6):1138–48.

Kausch I, Sommerauer M, Montorsi F, et al. Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies. Eur Urol. 2010 [cited 2016 Apr 20];57 (4):595–606. http://www.sciencedirect.com/science/article/pii/S0302283809012032

Kiragu D, Cifu AS. Evaluation of patients with asymptomatic microhematuria. JAMA. 2015;314(17):1865–6.

Lokeshwar VB, Habuchi T, Grossman HB, et al. Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. Urology. 2005;66 (6):35–63.

Mariappan P, Zachou A, Grigor KM. Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. Eur Urol. 2010;57 (5):843–9.

Massey BD, Nation EF, Gallup CA, Hendricks ED. Carcinoma of the bladder: 20-year experience in private practice. J Urol. 1965;93:212–6.

Mowatt G, N'Dow J, Vale L, Aberdeen Technology Assessment Review (TAR) Group, et al. Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: systematic review and meta-analysis. Int J Technol Assess Health Care. 2011;27(1):3–10.

O'Brien T, et al. Prospective randomized trial of hexylaminolevulinate photodynamic-assisted transurethral resection of bladder tumour (TURBT) plus single-shot intravesical mitomycin C vs conventional white-light TURBT plus mitomycin C in newly presenting non-muscle-invasi. BJU Int. 2013;112(8):1096–104.

Onkologie L. S3-Leitlinie Früherkennung, Nachsorge des Harnblasenkarzinoms. 2016;1–371.

Ozcan C, Telli O, Ozturk E, et al. The prognostic significance of preoperative leukocytosis and neutrophil-to-lymphocyte ratio in patients who underwent radical cystectomy for bladder cancer. Can Urol Assoc J. 2015;9(11–12):789–94.

Schlomer BJ, et al. Prospective validation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. J Urol. 2010;183(1):62–7.

Têtu B. Diagnosis of urothelial carcinoma from urine. Mod Pathol. 2009;22(2):53–9.

Tritschler S, Scharf KA. Validation of the diagnostic value of NMP22 BladderCheck test as a marker for bladder cancer by phtotodynamic diagnosis. Eur Urol. 2007;51:403–8.

Tritschler S, Strittmatter F, Karl A, Stief C. [Urine marker systems for diagnosis of urothelial cancer]. Urologe A. 2013 [cited 2015 Feb 10];52(7):965–9. http://www.ncbi.nlm.nih.gov/pubmed/23784678

Turco P, et al. Is conventional urinary cytology still reliable for diagnosis of primary bladder carcinoma? Accuracy based on data linkage of a consecutive clinical series and cancer registry. Acta Cytol. 2011;55(2):193–6.

Turner AG, Hendry WF, Williams GB, Wallace DM. A haematuria diagnostic service. Br Med J. 1977;2 (6078):29–31.

van Rhijn BWG, van der Poel HG, van der Kwast TH. Urine markers for bladder cancer surveillance: a systematic review. Eur Urol. 2005;47:736–48.

Wallace DM, Bryan RT, Dunn JA, Begum G, Bathers SW. West Midlands Urological Research G. Delay and survival in bladder cancer. BJU Int. 2002;89 (9):868–78.

Yang LP. Hexaminolevulinate blue light cystoscopy: a review of its use in the diagnosis of bladder cancer. Mol Diagn Ther. 2014;18(1):105–16.

Zheng C, Lv Y, Zhong Q, et al. Narrow band imaging diagnosis of bladder cancer: systematic review and meta-analysis. BJU Int. 2012;110(11):680–7.