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DIAGNOSIS OF NON-MUSCLE-INVASIVE BLADDER CANCER

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The most common form of bladder cancer is transitional cell carcinoma (developing from the transitional epithelium of the urinary tract), less common are squamous cell carcinoma and adenocarcinoma (a tumor derived from and built from the glandular epithelium). The main methods for diagnosing RMP are cystoscopy with biopsy. Modern radiological imaging helps to plan the treatment of localized kidney cancer, allowing the characterization of volumetric lesions. A CT-based radiomics prediction model can assess the muscle invasiveness of bladder cancer before surgery with good diagnostic performance. Bladder cytology gives the highest specificity and the NMP22 BladderChek urine marker test the highest sensitivity for high-grade tumors. Their combination appears to be the best approach for susceptibility to high-grade tumors compared to single markers and other combinations.

Keywords: non-invasive bladder cancer, ultrasound diagnostics, computed tomography, cytology.

Introduction

Bladder tumors are a heterogeneous group of cancers. The most common form of bladder cancer is urothelial carcinoma (developing from the transitional epithelium of the urinary tract), less common are squamous cell carcinoma and adenocarcinoma (a tumor derived from bladder mucosa, urachal, with exstrophy). The disease can manifest as papillary growths (nonlinear parietal inclusions) with malignancy or a solid, ulcerated, invading tumor. Bladder cancer includes cancer in situ (CIS) , superficial cancer (T1-2) and cancer that invades the muscle layer and surrounding tissues (T3-4).

The natural course of these types of bladder cancer is the recurrence of the disease and progression to a higher grade and stage of the disease. In addition, the recurrence and progression rate of superficial bladder cancer varies depending on several characteristics of the tumor, mainly tumor's grade and stage [1-5].

The latest World Health Organization (WHO) classification of urinary tract tumors includes urothelial squamous lesions: squamous hyperplasia, dysplasia, and carcinoma in situ [6, 7].

Papillary lesions are broadly classified into benign (urothelial papillomas and inverted papillomas), papillary urothelial neoplasia with low malignant potential (PUNLMP) and non-invasive papillary carcinoma (low or high grade) [1, 8-10].

The last WHO proposal for a classification of urinary tract tumors was implemented in 2004, and most reports confirm that the categories for this classification are better defined than previous classifications. An additional important issue is that PUNLMP, the most controversial WHO proposal in 2004, has a lower malignancy than low-grade carcinoma [11-13].

Whether PUNLMP will remain a clinically useful category or whether this category should be expanded to include all low-grade Ta lesions (PUNLMP and low-grade papillary carcinoma) as a broader category of less aggressive tumors not labeled as cancer [14-20] .

The classification of TNM adopted in 2009 by the International Cancer Union was revised in 2017 (8th edition), but the changes did not affect bladder tumors (Table 1.1) [21-25].

The bladder has a number of benign epithelial proliferations that are difficult to distinguish from carcinoma, including urothelial carcinoma and its variants, squamous cell carcinoma, and adenocarcinoma [24, 26–29].

In case of misdiagnosis, there is a possibility of overtreatment with an associated risk of complications, as well as errors associated with prognostic assessment [30-32].

If high-grade proliferative lesions that mimic invasive carcinoma are misdiagnosed, unnecessary radical surgery, chemotherapy, and radiotherapy may occur [11, 33, 34].

Similarly, misdiagnosis of lesions that look like low-grade carcinoma can lead to lifelong radiological examination and cystoscopy.

One of the initial signs of bladder cancer is hematuria (the appearance of blood in the urine), although it can be caused by other factors [27-29]. Blood clotting in the bladder cavity can lead to the development of acute urinary retention.

Another common symptom of the disease is frequent painful urination [80]. It is also possible the appearance of suprapubic pain.

Compression of the openings of the ureters by a tumor leads to a disorder of the passage of urine from the kidneys, as a result of which pyelonephritis or chronic renal failure may develop [30-31].

There is a known case of weekly priapism, which, as it later found out, was a symptom of the disease [32].

Cystoscopy with biopsy is considered to be the main diagnostic method for bladder cancer [33-36].

Additional diagnostic methods are excretory urography, computed tomography, ultrasound, etc. [37].

During clinical examination, bimanual palpation is mandatory, while it must be borne in mind that small tumors growing inside the bladder are usually not palpable. A palpable mass is indicative of a widespread penetrating lesion of the bladder [38,38,40].

To clarify the degree of infiltration of the bladder wall and its transition to the surrounding tissues, x-ray examination is sometimes used under double contrasting conditions, in which oxygen is injected into the bladder and into the surrounding tissue. Against the background of gas, one can see a thickening of the bladder wall and areas of tumor protrusion beyond its limits [40].

To determine or exclude metastases in the lungs, a chest x-ray is performed. If bone metastases are suspected, bone x-rays are done [41].

Among patients with newly diagnosed BC, the manifestation of gross hematuria is associated with a later pathological stage. Early detection of the disease before the development of gross hematuria may affect the survival of patients with bladder cancer. The type of hematuria at admission does not affect the severity of the disease [42].

A thorough physical examination is mandatory, although it does not allow the diagnosis of NIBC [43].

Transabdominal ultrasound is performed in addition to physical examination, since the method has a relatively high sensitivity in the diagnosis of various pathologies of the upper and lower urinary tract. Ultrasound can characterize kidney formations, identify hydronephrosis and intraluminal formations in the bladder, but does not rule out all possible causes of hematuria. In addition, ultrasound does not make it possible to exclude the presence of tumors in the upper urinary tract, and therefore cannot replace CT urography [44-46].

Computed tomography of the urinary organs is a modern method of X-ray diagnostic examination, which allows to identify a number of anomalies and pathologies of the urinary tract (ureters, bladder, urethra). CT scan of the bladder, performed by an experienced specialist, allows to determine the features of the structure and walls of the bladder, as well as adjacent tissues [47].

Modern radiological imaging helps to plan the treatment of localized kidney cancer, allowing the characterization of voluminous neoplasms. For patients with advanced kidney cancer, new imaging modalities allow for a functional assessment of response to treatment, which is not possible with anatomical measurements alone.

Multidetector CT urography allows simultaneous assessment of the condition of the kidneys and urinary tract in patients with unexplained hematuria. Both CT and MRI play an important role in the staging and follow-up of patients treated for urothelial cancer. New imaging modalities such as diffusion-weighted MRI have shown promising results for improving the accuracy of staging and surveillance of urothelial cancer [48].

CT urography is an reliable test for diagnosing bladder cancer. However, in the protocols of this method, based mainly on images of the excretory phase, the overall sensitivity remains insufficient to avoid cystoscopy. Awareness of imitation of the bladder cancer may reduce the number of false-positive results. Improvements in CT urography technique may reduce false negatives [49].

A CT-based radiomics prediction model can assess the muscle invasiveness of bladder cancer before surgery with good diagnostic performance [50].

Multiparametric MRI of the bladder has a high diagnostic efficiency in local staging of bladder cancer, surpassing other imaging methods. It can accurately differentiate muscle-invasive bladder cancer (MIBC) from NIBC, as well as stages </=T2 from >/=T3. Nodal and distant staging is primarily dependent on contrast-enhanced CT [51].

Subsequently observation of tumor in patients with NIBC presents weighing between the morbidity, associated with invasive diagnosis and the risk of tumor recurrence and especially progression. The division of risk into low, intermediate, and high risk tumors allows risk-based observation. Risk calculators should be used to individually assess the risk of progression and recurrence.

Observation is still based on cystoscopy, which is recommended for life for high- and intermediate-risk tumors, and for low-risk tumors, up to 5 years after tumor eradication. Urinary cytology has high sensitivity and specificity for high-risk tumors and is recommended for follow-up. There are currently no recommendations for any commercially available urinary marker due to insufficient evidence. To clarify synchronous and metachronous tumors of the upper urinary tract, computed tomography (CT) urography or alternatively magnetic resonance urography is recommended [52,59].

Bladder MRI may be the most useful in patients with NIBC, to expedite definitive treatment or to determine response to bladder-sparing approaches [53].

Apparent diffusivity measurements obtained by diffusion-weighted magnetic resonance imaging are a promising imaging biomarker for predicting the stage and grade of bladder cancer, providing high sensitivity and specificity. Further research is needed to establish the value of this test for decision making in clinical practice [50–54].

Imaging methods (excretory urography, CT urography, ultrasound or MRI) do not detect carcinoma in situ [55].

Although bladder cytology is the most widely used non-invasive test for detecting and monitoring bladder cancer, it has low sensitivity, especially for low-grade tumors.

Bladder cytology gives the highest specificity and the NMP22 BladderChek urine marker test the highest sensitivity for high-grade tumors. Their combination appears to be the best approach for increasing sensitivity to high-grade tumors compared to single markers and other combinations [56].

Blue light cystoscopy reveals a significantly greater number of tumor lesions, including carcinoma in situ and papillary carcinoma in the bladder. The use of a flexible blue-light cystoscope with hexaminolevulinate hydrochloride (compared to a white-light cystoscope) for observation slightly increases the cost to the practice with a difference of US$0.76 per cystoscopy over 2 years [57].

In 2016, the Paris Working Group published a standardized system for describing urine cytology (TPS) results [44] :

- The adequacy of the urine sample (adequacy),
- no high-grade urothelial carcinoma (negative),
- atypical urothelial epithelium (AUC).
- suspicion of high-grade urothelial carcinoma (suspicion),
- high-grade urothelial carcinoma (HGUC),
- low-grade urothelial carcinoma (LGUN).

For malignant urinary tract cytology specimens, the TPS criteria improved specimen risk stratification by elevating approximately 40% of indeterminate specimens to higher-risk categories without significantly changing the incidence of high-grade urothelial carcinoma diagnoses [53].

Biomarker efficiency requirements vary depending on the clinical scenario. The clinical role of urinary biomarkers in the observation of patients with NIBC remains uncertain. FDA-approved tests have unsatisfactory levels of sensitivity and specificity and their use is limited. Current commercially available urine biomarker tests are not sufficiently validated to be widely used in clinical practice. Several new biomarkers are currently being investigated. Prospective multicentre studies will be required to establish their clinical significance and value [59].

BCG therapy is the most effective drug for intravesical therapy. Despite the long study of BCG therapy, many unclear questions remain, and the results of various studies are often contradictory [55-57].

A positive fluorescent in situ hybridization test in patients with medium to high risk NIBC treated with BCG was correlated with a higher risk of tumor recurrence. Fluorescence in situ hybridization may assist urologists in risk stratification and patient counseling. The preferred time frame for fluorescent in situ hybridization is 3 months after TUR of the bladder tumor. This is also relevant for patients who received induction therapy, as it has not yet passed clinical trials or changed the treatment strategy [50].

A multicentre, prospective, blinded study was conducted at 21 European centers in patients undergoing cystoscopy for non-muscle invasive bladder cancer diagnosed within the previous 2 years. This large, blinded, prospective study demonstrates that follow-up of patients with non-muscle invasive bladder cancer using the ADXBLADDER protocol can rule out the most aggressive tumors with a negative predictive value of 99%. These results suggest that the ADXBLADDER protocol may be included in a follow-up strategy for the treatment of non-muscle invasive bladder cancer [57-58].

Urine samples from 440 patients under observation for NIBC were prospectively collected from five centers and evaluated using the Bladder EpiCheck test (NCT02647112). Data from 357 patients were available for analysis. The test had a specificity of 88% (95% confidence interval [CI] 84-91), a negative predictive value (NPV) of 94.4% (95% CI 91-97) for detecting any cancer, and an NPV of 99.3. % to detect high-grade cancer.

The Bladder EpiCheck is a reliable, high-performance diagnostic test in patients with NIBC under observation that has the potential to reduce the number of unnecessary tests [58-59].

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