Review aticle

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Morphological and molecular prognostic parameters in bladder cancer

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Bladder cancer (BC) is a worldwide disease, with an estimated global burden of over 614,000 new cases and over 220,000 deaths per year. Early, accurate diagnosis and an appropriate therapy approach are critical for reducing the mortality of BC. The histopathology diagnosis is crucial, and further therapy and prognosis are closely related to pathological criteria. BC is classified based on tumor lineage: urothelial, squamous, and glandular tumors, and according to the depth of invasion into non-invasive and muscle-invasive BC. All the BC subtypes have more aggressive behavior and a poorer prognosis than traditional urothelial BC (UBC). New molecular subgroup classification includes luminal-papillary, luminal-unstable, luminal-nonspecified, basal-squamous, stroma-rich, and neuroendocrine-like BC subclasses. Basal BC presents at a higher grade and advanced stage and is associated with shorter overall survival compared to other subtypes. Despite biological

aggressiveness, the basal BC phenotype shows higher sensitivity to cisplatin-based neoadjuvant chemotherapy and EGFR-targeted therapy. The most important prognostic parameters for non-invasive UBC are histological grade (low or high) and the occurrence of recurrence. In high grade UBC, recurrences occur in 60%, the rate of progression in the lamina propria is 25%, and in the muscle layer 5%. Overall mortality from UBC is associated with older patient age, male gender, invasive tumors, high grade UBC, tumors with divergent differentiation, and concomitant carcinoma in situ. Integration of artificial intelligence with molecular and genomic profiling data further supports personalized risk prediction and with great reliability can predict the response to different modalities of the therapy.

Key words: bladder cancer, prognostic parameters, recurrence, progression.

Pregledni rad

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Morfološki i molekularni prognostički parametri u karcinomu mokraćne bešike

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Karcinom mokraćne bešike je bolest rasprostranjena širom sveta, sa procenjenim globalnim opterećenjem od preko 614.000 novih slučajeva i više od 220.000 smrtnih ishoda godišnje. Rana, tačna dijagnoza i odgovarajući terapijski pristup su od ključnog značaja za smanjenje mortaliteta od carcinoma mokraćne bešike. Histopatološka dijagnoza je presudna, a dalja terapija i prognoza su usko povezani sa patološkim kriterijumima. Karcinomi mokraćne bešike se klasifikuju na: urotelijalne, skvamozne i glandularne tumore, a prema dubini invazije na neinvazivne i mišićno-invazivne karcinome bešike. Svi podtipovi karcinoma imaju agresivnije ponašanje i lošiju prognozu u poređenju sa tradicionalnim urotelijalnim karcinomom. Nova klasifikacija na osnovu molekularnih podgrupa uključuje: luminalno-papilarni, luminalno-nestabilni, luminalno-neodređen, bazalno-skvamozni, stromom bogati i neuroendokrini podtip karcinoma mokraćne bešike. Bazalni podtip se prezentuje u višem gradusu i uznapredovalom stadijumu, te je povezan sa kraćim ukupnim preživljavanjem u poređenju sa drugim podtipovima. Uprkos biološkoj agresivnosti, bazalni fenotip pokazuje veću osetljivost na neoadjuvantnu hemioterapiju baziranu

na cisplatini i na EGFR-ciljanu terapiju. Najvažniji prognostički parametri za neinvazivni karcinom mokraćne bešike su histološki gradus i pojava recidiva. Kod karcinoma visokog gradusa, recidivi se javljaju u 60% slučajeva, stopa progresije u laminu propriju iznosi 25%, a u mišićni sloj 5%. Ukupni mortalitet od karcinoma mokraćne bešike povezan je sa starijom životnom dobi pacijenata, muškim polom, invazivnim tumorima, visokim gradusom, tumorima sa divergentnom diferencijacijom i pratećim in situ karcinomom. Integracija veštačke inteligencije i podataka o molekularnom i genomskom profilu tumora podržava personalizovano predviđanje rizika i sa velikom pouzdanošću može predvideti odgovor na različite terapijske modalitete.

Ključne reči: karcinom mokraćne bešike, prognostički parametri, recidivantnost, progresija.

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Introduction

Bladder cancer (BC) is a worldwide disease, with an estimated global burden of over 614,000 new cases and over 220,000 deaths per year (1). It ranks as the seventh most frequent malignancy in the overall Serbian population and the 4th most common malignant tumor, after lung, colon, and prostate cancer in men. According to data from the Batut Institute, it is the 8th leading cause of death from malignant diseases in Serbia, with 2,500 new cases detected annually (2). BC includes a spectrum of tumors that are primarily classified according to the type of cells from which they arise and the depth of penetration into the bladder wall. Seven out of ten cases of BC are detected at an early stage. Recurrences are common and occur in 50-70% of cases, while progression can be expected in 15-25% BC (3). Superficial BC has an excellent prognosis, unlike BC that has invaded the muscle layer (4). The direct spread to the surrounding pelvic structures implies infiltration of the prostate, urethra, uterus, and vagina. Regional lymphogenic spread results in metastases in the obturator, presacral, iliac, and para-aortic lymph nodes. Through the hematogenous route, BC metastasizes to the liver, lungs, bones, and adrenal glands, and then the prognosis is poor (5). Non-muscle invasive (pTa) and early invasive BC (pT1) can be removed by transurethral resection (TUR), which is the first procedure for BC patients. The standard of care for intermediate-and high-risk non-muscle invasive BC remains intravesical therapy (i.e., Bacillus Calmette-Guerin - BCG, mitomycin). Radical cystectomy is the main surgical option in 30% of patients who present with muscle-invasive BC, while neoadjuvant or adjuvant chemotherapy reduces the risk of recurrence. External beam radiotherapy can keep localized disease under control. Metastatic disease has only a 5% five-year survival rate, and the treatment of choice is platinum-based chemotherapy (6). Newer therapies are based on immunotherapy, and the use of checkpoint inhibitors is the first line of therapy in the latest oncology protocols (7). Although survival rates have improved with early diagnosis, robotic surgical techniques, and the introduction of immunotherapy, BC remains a significant burden on the health care system worldwide. The cumulative costs per patient from the moment of diagnosis to the terminal stage of the disease make BC the most expensive malignancy for clinical monitoring and treatment (8). Early, accurate diagnosis and appropriate therapy approach are critical for reducing the mortality of BC. The

diagnosis of BC is carried out by pathologists through biopsy and further therapy and prognosis are closely related to pathological criteria (9).

Morphological prognostic parameters

The most recent World Health Organization (WHO) classification for BC is organized based on tumor lineage: urothelial, squamous and glandular tumors, however, according to pathology practice, broadly classified as urothelial (95%) and non-urothelial (5%). Urothelial bladder cancers (UBC) are classified based on architecture, morphology, and grade. Architecturally, they are divided into papillary, flat, and inverted lesions. Papillary lesions grow in an exophytic pattern as finger-like projections with a central fibrovascular core. All exophytic lesions have an endophytic counterpart (inverted lesions). The grade of a lesion is determined based on the level of atypia in the dysplastic urothelium. Typical/conventional urothelial pattern is the most common histology. Approximately 25% of UBC exhibit non-conventional histologies, which are generally associated with advanced stage at diagnosis and a more aggressive clinical course. Non-invasive UBC includes papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade (LG) papillary UBC, high-grade (HG) papillary UBC and urothelial carcinoma in situ (CIS). Urothelial proliferation with undetermined malignant potential is no longer a separate entity, and it is considered an early low grade non-invasive papillary urothelial carcinoma or extension at the tumor edge. Papillary tumors are considered HG if contain more than 5% HG component (10). Major morphological subtypes for muscle invasive UBC are micropapillary, nested, microcystic, plasmacytoid, sarcomatous, giant cell, lymphoepithelioma-like, with divergent differentiation (squamous, glandular, neuroendocrine, trophoblastic). Clear cell urothelial carcinoma (glycogen rich) and clear cell adenocarcinoma Müllerian type are different entities (11). All the subtypes have more aggressive behavior, with poor prognosis, then traditional UBC. They are considered significant prognostic parameters and must be included in the pathohistological report. Micropapillary presents with a tight cluster of cells, mimicking ovarian high grade serous carcinoma. It is highly aggressive subtype with early lymphovascular invasion and protocols suggest upfront radical cystectomy in pathologic (p) T1 stage. Plasmacytoid subtype consists of discohesive single cells mimicking plasma cells and spreading in linitis plastica manner, with a loss of E-cadherin as a key feature in

immunohistochemical (IHC) profile. Sarcomatous subtype has biphasic appearance with both epithelial and mesenchymal features (12). Both subtypes are extremely aggressive, with up to 60% patients in metastatic progression after first TUR. Neuroendocrine resembles neuroendocrine cancer elsewhere in the organism and expresses neuroendocrine markers like chromogranin and synaptophysin. It is a systemic disease from the start that requires specialized cisplatin/etoposide chemotherapy similar to lung cancer protocols (13). Pure squamous carcinoma without any component of conventional urothelial carcinoma is a very uncommon subtype of BC and must be distinguished from UBC with squamous differentiation, secondary spread of squamous cell carcinoma primary to another site, e.g., cervix, penis, anus, due to different therapy approach. Predisposing factors for non-urothelial BC include Schistosoma, Proteus mirabilis and Escherichia coli infections, smoking, urolithiasis, previous intravesical BCG therapy, pelvic radiation therapy, and prolonged exposure to cyclophosphamide (14, 15). There is increasing evidence of a correlation between EBV and HPV infection and squamous cell carcinoma (16). Adenocarcinomas make up about 2% of primary bladder malignancies. About two-thirds of the cases occur in the bladder trigone or posterior walls. The remainder, one-third, arises in the urachal remnants, usually near the dome. Microscopically, adenocarcinoma of the bladder can show a variety of morphologic patterns, including enteric (intestinal) type, colloid, signet-ring, hepatoid, non-specific (adenocarcinoma, NOS), and mixed patterns. The vast majority of adenocarcinomas are associated with the invasion of the muscle layer (pathologic stage pT2) by the time the patient becomes symptomatic. Urachal abnormalities, bladder exstrophy, cystitis glandularis or intestinal metaplasia within the bladder lining are favoring factors (17). Both adenocarcinomas and squamous cell BC have aggressive biologic behavior and are detected in advanced stages when the treatment options are limited.

Molecular prognostic parameters

The methods for diagnosing and treating localized and advanced diseases have changed as a result of advances in understanding of the molecular biology and genetics of BC. Accordingly, a new molecular subgroup classification has emerged. This classification includes luminal-papillary (24%), luminal-unstable (15%), luminal-nonspecified (8%), basal-squamous (35%), stroma-rich

(15%), and neuroendocrine-like BC subclasses (3%) (18). According to some authors and using next-generation sequencing UBC is divided into three molecular subtypes: luminal, basal, and p53-wild-type (19). Each subtype reveals diverse clinical behavior and different rate of response to immunotherapy and conventional chemotherapy. The basal UBC phenotype is characterized by a gene expression signature similar to the basal layer of normal urothelium, and frequently have histological feature of divergent differentiation. The phenotype can be identified by the IHC expression of CK HMW, CK5/6, CK14, and CD44. Basal UBC presents at a higher grade and advanced stage, and is associated with a worse clinical prognosis and shorter overall survival compared to other subtypes (20). Despite biological aggressiveness basal tumors show higher sensitivity to cisplatin-based neoadjuvant chemotherapy and EGFR targeted therapy (21). The luminal UBC phenotype mimics the differentiated intermediate and superficial layers of the normal urothelium. In morphology manner luminal UBC presents with papillary, micropapillary and nested features. Immunohistochemical expression of GATA3, HER2, CK20 and uroplakins and activated *PPAR*-γ and *FGFR3* mutations are key characteristics of this molecular subtype. Further molecular classification subdivides the luminal phenotype into distinct categories based on their clinical and genomic behavior as luminal-papillary, luminal-infiltrated ("p53-like") and luminal-unstable. It is generally associated with a more favorable prognosis than the basal phenotype, although "p53-like" and luminal-unstable subsets can be cisplatin resistant. High rates of *FGFR3* mutations make these patients primary candidates for FGFR inhibitors and may have good response to immune checkpoint inhibitors (22). The p53-wild-type (p53-WT) UBC retains functional *TP53* tumor suppressor gene. It is characterized by high rates of *FGFR3* mutations and genomic stability and presents as papillary non-muscle-invasive UBC. Despite having a p53-WT signature, these UBCs are notoriously resistant to cisplatin-based neoadjuvant chemotherapy and are considered for early immunotherapy (23). The most recent meta-analyses emphasize that identifying UBC subtypes through simple immunohistochemistry using GATA3 and CK5/6 allows 90% accuracy in subtyping and facilitate personalized treatment (24).

Risk of recurrence and progression of bladder cancer

The most important prognostic parameters for non-invasive UBC are histological grade and occurrence of recurrence. In HG UBC, recurrences occur in 60% and the rate of progression in the

lamina propria is 25%, while in the muscularis propria 5%. Multiple or large neoplasms (>5cm), previous recurrences, associated carcinoma in situ (CIS), and a shorter disease-free interval are factors associated with a higher risk of UBC recurrence (25). In HG UBC, marked nuclear anaplasia is associated with a shorter time to recurrence and progression. A high Ki-67 proliferation index combined with p53 expression may predict the risk for recurrence and progression, although IHC markers are not performed in routine practice (26). Normally, CK20 is expressed only in the superficial (umbrella-cell) layer. Abnormal CK20 full-thickness epithelial staining in UBC correlates with disease recurrence (27). Although molecular studies have improved the understanding of the biology of UBC, no single marker has been shown to be sufficiently prognostic to enter routine clinical practice. Female gender is associated with a higher risk for disease recurrence, progression and mortality after applied therapy (28). Data supporting androgenic regulation of cellular metabolic detoxification suggest the possibility of a two-hit event to explain the more frequent occurrence of UBC in men, and differential expression of enzymes responsible for carcinogen metabolism, including those in cigarette smoke. Sex steroids as a potential mechanism for the formation of UBC can be explained by the expression of the enzyme 5a-reductase, which converts testosterone to the more potent androgen dihydrotestosterone, which was detected in UBC. IHC analysis of tissue microarrays of 224 UKMB samples found that estrogen receptor (ER) is expressed in UBC in 63%, and expression increased with higher pathological stage (29). Women at increased risk for UBC have been observed to have an N-acetyltransferase-2 slow acetylation phenotype. Contrary to ER expression, androgen receptor (AR) expression decreases with increasing pathological stage. AR expression is significantly lower in pT2 tumors than in pTa and pT1 tumors, and in HG compared to LG tumors. A recent meta-analysis of 15,215 patients with HG pT1 UKMB showed that female gender was associated with a significantly higher risk of disease progression and recurrence (30). *FGFR3* mutations are common in noninvasive LG papillary UBC and are associated with a lower recurrence rate. *PTEN* deletions are associated with an increased recurrence rate in LG UBC. Recurrences are more common in patients treated with TUR alone, and less frequent in patients treated with TUR and intravesical BCG instillation, radiotherapy, and radical cystectomy (31). Disease progression is relatively rare in LG UBC, and molecular changes associated with increased risk for progression in pTa UBC include accumulation of p53, loss of nuclear p63 expression, loss of membrane expression of E-cadherin, and RB deletions.

Chromosomal alterations 3p, 4p, 5p, 5q, 6q, 10q, 18q, and LOH 16p13 are also predictors of progression to muscle-invasive UBC. Overall mortality from UBC is associated with older patient age, male gender, invasive tumors, HG UBC, tumors with divergent differentiation, and concomitant CIS (32).

Evidence based medicine shows that deep learning (DL) algorithms applied to cystoscopy improve lesion detection, including subtle flat and early-stage tumors that may be overlooked by conventional assessment. Artificial intelligence (AI) systems contribute to grading, classification, and identification of malignant features with accuracy comparable to expert pathologists. Integration of AI with molecular and genomic profiling data further supports personalized risk prediction and very precise tumor characterization (33). Furthermore, DL has been shown to predict the expression of differential genes or molecular biomarkers such as PD-L1 and FGFR, and with great reliability can predict the response to different modalities of therapy (34).

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