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URINARY AND TISSUE BIOMARKERS IN EARLY DETECTION OF UPPER UROTHELIAL TRACT CANCER

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Summary. *Upper urothelial tract cancer (UUTC) is an uncommon disease presenting only 5 to 6% of all urothelial tumors. In families affected with Balkan endemic nephropathy the incidence is 100 times greater. The most common symptom of UUTC is hematuria (75%) and flank pain (30%). Excretory urography is still the first choice examination in the exploration of hematuria. Urinary cytology testing has a high specificity (over 90%) but low sensitivity (below 50%). Flexible or rigid ureteroscopy enables taking biopsies and confirms the diagnosis with a sensitivity over 80% but with a low specificity of about 60%. This diagnostic procedure does not permit an early diagnosis, and could miss UUTC. However, the better understanding of the molecular mechanisms involved in carcinogenesis and tumor progression has provided a large number of molecular markers of UUTC, with a potential diagnostic and prognostic value. The characterization of the molecular features of urothelial carcinomas is still ongoing. The goal is to relate the tumor genotype to am individual's phenotype and to discover a specific diagnostic marker associated to the tumor's molecular biology. If an at-risk genetic profile could be established, it might be possible to predict, even prevent urothelial carcinomas in some patients. Further investigations are needed in order to find the best marker for early detection of UUTC. The ideal UUTC test is still unavailable, but the eventual "gold standard" will consist of multiple assays that analyze nucleic acids and proteins for detection. In addition, these tests would also reveal to the clinician both prognostic information and therapeutic targets for personalized medical treatment.*

Key words: *Upper urothelial tract cancer, biomarkers, diagnosis, prognosis*

Introduction

Transitional cell carcinoma of the upper urinary tract is an uncommon disease presenting only 5 to 6% of all urothelial tumors. Upper urothelial tract cancer (UUTC) rarely occurs before the age of 40, having the peak incidence in the fifties. UUTC are three times more prevalent in men than in women. In families affected with Balkan endemic nephropathy the incidence is 100 times higher (1).

Various histopathological and clinical parameters are known to have prognostic significance in UUTC. These parameters include tumor stage, histological grade, multicentricity, tumor growth pattern (papillary vs. solid), carcinoma in situ of the adjacent urothelium, and tumor cell proliferation. The current treatment is based on the pathological staging of the tumors. While histopathological criteria can provide important morphological information about tumors, they are not reliable to specify the risk for progression or response to treatment for a patient with UUTC.

The most common symptom of UUTC is hematuria (75%) and flank pain (30%). Excretory urography is still the first choice examination in the exploration of hematuria. Ultrasonography is helpful in distinguishing between UUTC and calculosis. CT scan may be useful in diagnosing and in staging renal parenchymal tumors, but it is difficult to diagnose small volume tumors of the renal pelvis and urether. Urinary cytology testing has a high specificity (over 90%) but low sensitivity (below 50%). Flexible or rigid ureteroscopy enables taking biopsies and confirms the diagnosis with a sensitivity over 80% but with a low specificity of about 60%. Cystoscopy is used to examine patients with painless hematuria or irritative voiding, symptoms that are often related to urinary tract infection or benign prostatic hyperplasia. Cytological examination of urine is specific and noninvasive, comparing to cystoscopy. It has good sensitivity for detection of high-grade bladder cancers, but poor sensitivity for low-grade cancers (1, 8, 9). This diagnostic procedure does not permit an early diagnosis, and could miss UUTC.

There are several diagnostic tests for bladder carcinoma (used also in UUTC), which detect the presence of specific tumor product in urine samples, such as the original bladder tumor antigen (BTA) test, immunoCyt, the detection of nuclear matrix protein 22, Vascular endothelial growth factor test, Telomerase test, Hyalu-

ronic acid test, detections of the specific cytokeratins 18, 19, and 20, LCA4, Lewis X, CD44 and mucin 7 detection (5).

The initiation of DNA replication represents a potentially attractive target for diagnostic analysis. Proteins of the minichromosome maintenance (Mcm) family (Mcm2, Mcm3, Mcm4, Mcm5, Mcm6, and Mcm7) play a regulatory role in the initiation of DNA replication. These findings were used for detection of cervical cancer. MCM proteins distinguish proliferating and non-proliferating cells and their expression is a more sensitive marker of epithelial carcinogenesis than expression of conventional proliferation markers. The Mcm5 test was significantly more sensitive than urine cytology, 73% versus 48%. The fraction of Mcm5-expressing cells in urothelial carcinoma is associated with the pathological grade of transitional cell carcinoma, 78% for poorly differentiated G3 tumors, 70% for moderately differentiated G2 tumors, and 45% for well differentiated G1 tumors (2).

Urine analysis as noninvasive diagnostic procedure

The limited value of the established markers demands analysis of new molecular parameters having the potential to be used for an early diagnosis and in prevention of UUTC. Since urine contains various metabolites, but also washes out urothelial cells and its protein products throughout urinary tract, a concept of analyzing urine in order to detect diseases, has been developed (12).

In the early stages of carcinogenesis, most of the aberrant cells have no apparent growth advantage, but some genetic or epigenetic defects may be present in multiple clones of cells. Therefore, it would be useful to define these changes existing at the early stage, making it possible to prevent the disease progression. Tumorigenesis is a multistep process that results from the accumulation and interplay of genetic mutations and epigenetic changes (12).

Genetic modifications

Due to complex interactions and genomic instability of the cancer cells it is challenging to identify changes found in UUTC that are fundamental to the malignant process. Such new parameters may be derived from our increasing knowledge on the molecular alterations in these tumors. The complex regulation of the protein expression at gene, transcriptional, translational and post-translational levels makes the finding of highly specific biomarkers for a particular disease, an extremely hard task. Genetic analyses of UUTC tumors will prove that hereditary background could help in facing the daunting task of searching through the large number of indentified genetic variants associated with malignant transformation, to identify the few among them that are involved in the etiology, providing us with valuable biomarkers. Because of the similarities between UUTC and bladder transitional cell carcinoma (TCC) with regard to etiology, histology, and natural disease history, one would assume that the tumorigenic mechanisms, including the karyotypic profile, are more or less identical.

Multifocal occurrence and frequent recurrence are characteristic for urothelial carcinomas of the urinary bladder and the upper urinary tract. The majority of studies revealed a monoclonal origin of the multiple tumors. Oligoclonal tumors might be more common in precursor lesions and early tumor stages. The frequent monoclonality found in patients with advanced tumors could be due to outgrowth of 1 tumor cell clone with specific genetic alterations. Superficial papillary tumors have been shown to be relatively genetically stable and the alterations found suggest that in all cases, multifocal tumors share a common origin (24).

Hypermethylation at 11 CpG islands in upper urinary tract transitional cell carcinomas (UTTC) and lower tract urothelial carcinomas was reported. Despite morphological similarities between these cancers, a more extensive promoter hypermethylation was found in UTTC (96%) than UCs (76%). Methylation of any one of DAPK, RARß, E-cadherin, p16 could be detected in 90.9% of the urine samples, whereas urine cytology was able to detect cancer cells in only 45.5% of the samples. The negative side of this method is that methylation could only be detected in those patients whose tumor tissue also showed gene methylation. No methylated copies of E-cadherin, DAPK, or p16 were detected in normal urine (100% specificity) (11).

Microsatellites are highly polymorphic short tandem DNA repeats found throughout the human genome. Two types can be present in many cancers. One is loss of heterozygosity (LOH), which can be detected in exfoliated cancer cells in urine, as well as bladder tumor tissues. The other is a somatic alteration of the microsatellite repeat in cancer cells, which can be detected as microsatellite instability (MIS). They can be used as markers of neoplasia and are known as 'microsatellite alterations'. Micronuclei can be detected in exfoliated cells of the buccal mucosa, urinary bladder, cervix or bronchi and seem to reflect chromatid and chromosome aberrations which occurred in the proliferating basal layers. The MN assay has been a preliminary indicator for precancerous lesions (3). The sensitivity and specificity for UUTC isn't yet explored.

Numerous chromosomal deletions have been detected in bladder cancer. Genomic studies have shown that the most frequently deleted chromosomal regions in bladder cancer are 2q, 4q, 5q, 6q, 8p, 9p, 9q, 11p, 11q and 13q, and the most frequently over-represented are 1q, 3p, 5p, 6p, 8q, 17q, and 20q. Some of the regions contain tumor suppressor genes and oncogenes, already known to be involved in bladder cancer development. Those are erbB-2, EGFR, c-myc, HRAS, p53, RB-1,CdkN2 (25, 10). Except for deletions in chromosome 9, these deletions are found in high grade, high stage bladder cancer.

Homozygous deletion and loss of heterozygosity in 3p21.3 genes including transcriptional silencing by

promoter hypermethylation, altered mRNA splicing and aberrant transcripts, lost or defect protein translation and post-translational modifications, is found in most human cancers. Inactivation of 3p21.3 genes in tumors affects cell proliferation, cell cycle kinetics, signaling transduction, ion exchange and transportation, apoptosis. Deletions on chromosome 3p are associated with invasive tumors. Two genomic regions have been identified that are most frequently deleted, 3p12-14 and 3p21-23. Chromosomal translocation from 3p14.2 to chromosome 8q24 was suggested to affect a tumor suppressor gene. In bladder cancer, reduced expression of gene Fragile Histidine Triad (FHIT) has been correlated with promoter hypermethylation (6). There is a suggestion that these findings can be applied in UUTC detection.

Deletions of the short arm of 8 chromosome are correlated with cancer progression, tumor grade, stage and invasiveness. There are four known putative tumor suppressor genes in this region, LZTS1 (leucine zipper putative tumor suppressor 1), DBC2 (deleted in breast cancer 2), DLC1 (deleted in liver cancer 1) and FGL1 (fibrinogen-like 1), but they haven't been further investigated in UUTC (18).

Chromosome 13 harbors the Retinoblastoma tumor suppressor at 13q14. Alterations of p53 and Rb are found in the same tumors. Deletions of 17p have been identified in almost every cancer studied. The most prominent tumor suppressor is p53. Together with Rb, p53 plays a role in DNA damage, apoptosis and cell cycle to redox regulation and ageing (18).

Mutations of p53 are the most common genetic defects in human tumors, including bladder cancer. Nuclear accumulation of p53 detected by immunohistochemical staining correlates with increased p53 mutations in DNA sequence analysis. Increased p53 nuclear reactivity is associated with bladder cancer progression, increased recurrence, decreased overall survival, decreased responsiveness to chemotherapy, higher grade, and higher stage of urothelial carcinoma (18).

Recently the cell cycle has been shown to be important in tumour proliferation and in determining the prognosis of patients with cancer. Cell-cycle progression is governed by the sequential formation and degradation of a series of cell-cycle regulating cyclins. p27Kip1 (p27) is a negative cell-cycle regulating gene that codes a cyclin-dependent kinase inhibitor and is thought to be an essential part of the transition from the late G1 phase to the S phase. Low levels of p27 protein are reported to be a negative prognostic factor in breast, lung, gastric, colorectal and prostate cancer. Reduced levels of p27 also correlate with higher stage and shortened survival in TCC of the bladder. Kamai et al showed that there was no significant association between p27 immunohistochemically staining and grade or tumour proliferation (Ki-67 index) in TCC of the upper urinary tract, whether p27 levels correlate with these conventional prognostic factors (16).

Superficial papillary urothelial tumours of the bladder in young patients had a better prognosis than those in the elderly group, showing a lower grade and stage at diagnosis, and a lower recurrence rate. Proliferative activity and cyclin D1 expression levels were of prognostic significance for the risk of recurrence in these patients (19).

Ioachim et al. examined the expression pattern of cyclins D1 and E, as well as cyclin-dependent kinase inhibitors p21(Wa1/Cip1) and p27(Kip1) and their relationship to tumour behaviour and patients' prognosis in urothelial cell carcinomas of urinary bladder. They concluded that the level of the cell cycle regulators studied does not seem to have a clinical value in terms of predicting the risk of early recurrence and progression. In addition, the interrelationship probably means their contribution to the regulation of cell growth through different pathways in bladder carcinogenesis (17).

Loss of chromosome 9 has been the only chromosome loss at the early tumor stages T0 and T1. Loss of the entire chromosome 9 represents an initial event in bladder tumor formation. The four discovered deleted loci on the long arm of chromosome 9 harbor 3 putative tumor suppressor genes. An investigation of p15 and p16 expression in superficial and invasive bladder cancer revealed a significantly lower expression of p15 in superficial but not in muscle invasive bladder cancer suggesting that loss of p15 contributes to the tumor type but not to progression (10).

Loss of the Y chromosome is common in bladder tumors of male patients. It has been detected in all stages in several reports. In contrast, bladder tumors in females don't show the same incidence of X loss (10).

The contents of these chromosome deletions are mostly tumor suppressor genes, which cause uncontrolled cell grown. Further investigations of UUTC genetic modifications should find consequences of these deletions in order to understand cancerogenesis processes.

Bladder cancers are classified into two types according to genetic instability: microsatellite instability (MSI) cancers showing good prognosis and chromosomal instability (CIN) cancers that show highly malignant potential. Defects in mismatch repair genes, including hMLH1 and hMSH2, lead to MSI. MSI accounts for 10% to 20% of sporadic colorectal carcinomas but the frequency of MSI in bladder cancer isn't established. CIN results from abnormalities of genes implicated in mitosis. Centrosome amplification, over expression of STK15/ BTAK/Aurora-A kinase located on 20q13, p53 mutation and cyclin E over expression are linked with CIN (15).

Epigenetic changes

Pre-mRNA splicing is a nuclear process. Intronic splice site mutations of tumor suppressor genes often cause exon-skipping events. Affected proteins may include transcription factors, cell signal transducers, and components of the extracellular matrix. Mutations can cause aberrant splicing by making an inappropriate

creation of cryptic splice site signals. The definition of alternative splicing is the process whereby identical pre-mRNA molecules are spliced in different ways, and this is important in normal development as a means of creating protein diversity in complex organisms. Many alternative splicing events have been noted in human development, especially in the brain and the testes. In cancer there are examples of every kind of alternative splicing, which include the use of alternative individual splice sites, alternative exons and introns. Alternative splicing in small cell lung cancer involves the mutually exclusive use of alternative exons, and a mutually exclusive splice of the cytoskeletal protein actinin-4. The extra exon is a potential clinical marker for this cancer. Soluble cell signaling adaptor proteins are involved in the spread of cancer, and several cellular factors involved in the transduction of oncogenic signals are alternatively spliced in specific cancers: medulloblastomas and primitive neuroectodermal tumors, colorectal cancer, glioblastoma, etc. Transmembrane receptor proteins are essential for transmitting growth signals from the extracellular matrix, and several are alternatively spliced in cancer. Specific variants of two G-protein–coupled receptors have been found in pancreatic tumors. The growth-inhibitory secretin receptor without exon 3 has a 36 amino acid deletion, and this was the predominant form in pancreatic tumors. Several proteins involved in cell adhesion are alternatively spliced in cancer. The tumor suppressor and cell adhesion molecule C-CAM1 has a short frame-shifted form lacking exon 7, which encodes its cytoplasmic domain that is implicated in insulin receptor signaling. The most studied alternatively spliced gene in cancer is CD44, which is a transmembrane protein involved in cell-cell adhesion. CD44 has 20 known isoforms due to variable incorporation of 10 alternative exons in its proximal extracellular domain (7).

It was proven that it is difficult to use these genetic alterations as diagnostic markers of bladder cancer because of their low sensitivity. But these findings could be an important source in exploring different options for early carcinoma detection in upper urothelial tract. Investigation of alternative splicing could lead to discovery of special protein products which could be used in developing prevention protocols.

The molecular pathways leading to apoptosis are evolutionarily conserved and controlled by caspases proteins either promoting or inhibiting the activation of a cascade of intracellular cysteine proteases. Caspase activity is inhibited by the inhibitor of apoptosis (IAP) family. X-linked IAP (XIAP), whose gene is located at Xq25,9 demonstrates significant inhibition of apoptosis. Over expression of IAPs protects tumors cells in vitro from apoptosis induced by different anticancer drugs. IAPs promote tumor progression in vivo, suggesting that it might be used as the novel prognostic factors. Over expression of XIAP was found in bladder cancer. XIAP might act as a new independent diagnostic and prognostic marker of non-muscular invasive bladder carcinoma, but it could be used for UUPC detection in early stage (13).

Analysis of apoptosis and p53 status of the UUTC from Balkan endemic nephropathy regions showed higher degrees of apoptosis in UUTC with extreme cell atypia (grade 3). In addition, in endemic regions proliferation does not dramatically increase with UUTC progression to high grade, UUTC slowly grows in conditions of surrounding ischemia. Authors suggested that chronic ischemia may facilitate triggering of apoptosis in a tumor (20).

TERE1, a recently discovered gene/protein appears to play a role in bladder tumor growth regulation but to date does not have clear functional correlates. The TERE1 gene has been localized at chromosome 1p36 and the TERE1 transcript is generally expressed in normal human tissues including urothelium. The TERE1 transcript was under-expressed in muscle invasive TCC tumors. Normal bladder mucosa and bladder tumor specimens contain the apoE protein. ApoE is expressed by normal and malignant urothelium including TCC cell lines. In the kidney, apoE has been found to regulate mesangial cell proliferation and may partially regulate proliferation in the bladder. Recent reports have linked either apoE transcript or apoE protein over expression in ovarian and prostate cancer. There is an apparent interaction between TERE1 and ApoE. Both proteins control cellular proliferation and their interaction could enhance cell cycle arrest. Defined knockouts and functional assays may determine if the interaction between TERE1 and ApoE has a role in growth-related signal transduction pathway in carcinoma cells, and if this interaction could be used in investigating UUTC (14).

A family of zona pellucida (ZP) domain proteins is characterized by the presence of a single ZP domain which was first recognized in three glycoproteins (ZP1, ZP2 and ZP3). ZP domains were identified in several other glycoproteins such as TGF-b receptor type III, uromodulin, the major granule membrane glycoprotein GP-2 and in more than 100 other proteins. ZP proteins have been detected in soluble form but they can also behave as integral membrane receptors. Hensin, a secreted ZP protein in rabbit collecting ducts of the kidney, induces a reorganization of the apical membrane and its associated cytoskeleton leading to columnarization of intercalated cells. Many ZP proteins that were characterized in various organisms were shown to be essential for epithelial morphogenesis. It would be interesting to explore their presence in cancer cell during cancerogenesis, and potential role in detection of malignancy in upper urinary tract (23).

Cell adhesion is an elementary process in the establishment of tissue architecture and differentiation. In neoplasia, in which there is a disruption of this process, it has been postulated that changes in cell-cell and cell-matrix interactions show the ability of cancer cells to transgress normal tissue boundaries and disperse. Complex reductions and increases in adhesion have been necessary for tumor invasion and metastasis. These

moleculs, involved in cell adhesion process, have an important role in cell signaling. Alterations of expression of the cytoskeletal proteins Gelsolin and E-cadherin (E-CD) have been implicated in urothelial carcinoma tumorigenesis. It is not clear how these altered expressions associate with tumor progression. CIS and superficial, noninvasive papillary TCC strongly express E-CD. Loss of E-CD expression is associated with the invasive TCC phenotype. Actin remodeling is the result of activation of oncogenic actin signaling pathways (e.g., Ras and Src), or inactivation of several important actin-binding proteins that have tumor suppressor functions (gelsolin). Actin dynamics are regulated by a complex interplay of the small GTPase proteins of Ras superfamily Rac, Rho, and Cdc42 (26).

Screening

Since the incidence of UUTC is very low, screening the whole population wouldn't have an adequate cost-benefit ratio. Though, it would be cost-effective developing a cost-effective protocol for screening in endemic territories. One of the important goals for researchers should be finding a urinary biomarker test that enables early detection of UUTC with high sensitivity and specificity, and, at the same time, easy to perform and cheap enough.

Treatment

The first choice for treating UUTC is nephroureterectomy with bladder cuff excision, except in cases of solitary kidneys, bilateral disease or renal dysfunction when nephron-sparing surgery is being performed. Five-year survival and recurrence rate in case of sparing procedures, correlates with the tumor stage (21). Therefore, there is an urge to find a biomarker for UUTC which would be positive at early stages and increase the survival rate in patients with UUTC (especially after conservative treatment).

Researches in UUTC genomics and proteomics do not help only in search for a valuable marker, but also for a potential therapeutic target. Until now, none of the trials performed has shown to be effective (intravesical administration of replication-defective adenoviral particles that encode wild-type p53, administration of farnesyl transferase, EGFR and HER2/neu inhibitors). MAK and FGFR3 kinase inhibitors are on trial (data still not available), while suberoylanilide hydroxamic acid (SAHA) - histone deacetylases inhibitor has exhibited tumor response in a small number of patients treated (22). However, there are certainly proteins whose function is crucial for carcinogenesis, and its blocking or silencing of the encoding gene would lead to tumor cell cycle arrest and apoptosis.

Conclusion

The characterization of the molecular features of urothelial carcinomas is still ongoing. The goal is to relate the tumor genotype with individual's phenotype and to discover a specific diagnostic marker associated to the tumor's molecular biology. If an at-risk genetic profile could be established, it might be possible to predict, even prevent urothelial carcinomas in some patients. Further investigations are needed in order to find the best marker for early detection of UUTC, but also a potential therapeutic target.

References

1. Oosterlinck W, Solsona E, van der Meijden APM et al. EAU Guidlines on diagnosis and treatment of upper urinary tract transitional cell carcinoma. Eur Urol 2004; 46: 147-154.
2. Stoeber K, Swinn K, Prevost AT et al. Diagnosis of genito-urinary tract cancer by detection of minichromosome maintenance 5 protein in urine sediments. J Natl Cancer Inst 2002; 94: 1071-1079.
3. Gandhi G, Sharma P, Kaur A. A comparison of the urothelial cells and cervix scraping techniques in the screening process for cancer of the cervix. J Hum Ecol 2002; 17: 129-135.
4. Venables J. Aberrant and alternative splicing in cancer. Cancer Res 2004; 64: 7647-7656.
5. 5. Liou LS. Urothelial Cancer biomarkers for detection and surveillance. Urology 2006; 67 (suppl 3A): 25-34.
6. Li L, Minna JD, Roth JA. 3p21.3 Tumor suppressor cluster: prospects for translational applications. Future Oncol 2005; 1: 79-92.
7. Miyake H, Hara I, Kamidono S et al. Multifocal transitional cell carcinoma of the bladder and upper urinary tract: molecular screening of clonal origin by characteizing cd44 alternative splicing patterns. J Urol 2004; 172: 1127-1129.
8. Black PC, Brown GA, Dinney CP. Molecular markers of urothelial cancer and their use in the monitoring of superficial urothelial cancer. J Clin Oncol 2006; 24: 5528-5535.
9. Habuchi T. Origin of multifocal carcinomas of the bladder and upper urinary tract: Molecular Analysis and clinical implications. International Journal of Urology 2005; 12 (8): 709-716.
10. Fadl-Elmula I. Chromosomal changes in urothelial carcinomas. Cell & Chromosome 2005; 4: 1-9.
11. Kim WJ, Kim YJ. Epigenetic markers for bladder cancer in urine. Translational Oncogenomics 2007; 2: 35-42.
12. Leppert JT, Shvarts O, Kawaoka K et al. Prevention of bladder cancer: A review. European Association of Urology 2006; 49: 226-234.
13. Ming L, Tao S, Zhen-fei Y et al. XIAP as a prognostic marker of early reccurence of nonmuscular invasive blader cancer. Chin Med J 2007; 120: 469-473.
14. McGarvey TW, Nguyen TB, Malkowicz SB. An Interaction Between Apolipoprotein E and TERE1 With a Possible Association With Bladder Tumor Formation. J of Cellr Biochem 2005; 95: 419-428.
15. Yamamoto Y, Matsuyama H, Kawauchi et al. Biological characteristics in bladder cancer depend on the type of genetic instability. Clin Cancer Res 2006; 12: 2752-2758.
16. Kamai T, Takagi K, Asami H et al. Prognostic significance of p27Kip1 and Ki-67 expression in carcinoma of the renal pelvis and ureter. BJU Int 2000; 86: 14-19.
17. Ioachim E, Michael M, Stavropoulos NE et al. Expression patterns of cyclins D1, E and cyclin-dependent kinase inhibitors p21(Waf1/Cip1) and p27(Kip1) in urothelial carcinoma: Correlation with other cell-cycle-related proteins (Rb, p53, Ki-67 and PCNA) and clinicopathological features. Urol Int 2004; 73: 65-73.

18. Burchardt M, Burchardt T, Shabsigh A et al. Current concepts in biomarker technology for bladder cancers. Clin Chem 2000; 46: 595-605.
19. Migalde M, Rossi G, Maiorana A et al. Superficial papillary urothelial carcinomas in young and elderly patients: a comparative study. BJU Int 2004; 94: 311-316.
20. Petronic V, Savin M. Apoptosis and p53 status of the upper urothelial carcinomas from Balkan endemic nephropathy regions. Nephrol Dial Transplant 2001; 16: 33-35.
21. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol 2000;164:1523–1525.
22. Thomas CY, Theodorescu D. Molecular markers of prognosis and novel therapeutic strategies for urothelial cell carcinomas. World J Urol 2006;24:565–578.
23. Jazwinska A, Affolter M. A family of genes encoding zona pellucida (ZP) domain proteins is expressed in various epithelial tissues during Drosophila embryogenesis. Gene Expr Patt 2004; 4: 413–421.
24. Hafner C, Knuechel R, Stoehr R. Clonality of multifocal urothelial carcinomas: 10 years of molecular genetic studies. Int J Cancer 2002; 101: 1 – 6.
25. Zaharieva B, Simon R, Diener Pierre-Andre High-throughput tissue microarray analysis of 11q13 gene amplification (CCND1, FGF3, FGF4, EMS1) in urinary bladder cancer. Int J Cancer 2003; 201: 603 –608.
26. Rao Jy, Seligson D, Visapaa H, et al Tissue microarray analysis of cytoskeletal actin-associated biomarkers gelsolin and E-cadherin in urothelial carcinoma. Cancer 2002;95:1247-57.

URINARNI I TKIVNI BIOMARKERI U RANOJ DIJAGNOSTICI KARCINOMA GORNJEG URINARNOG TRAKTA

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Kratak sadržaj: *Karcinom gornjeg urinarnog trakta (UUTC) je retko oboljenje koje predstavlja samo 5 do 6% svih urotelijalnih tumora. Incidenca tumora je 100 puta veća u porodicama obolelih od Balkanske endemske nefropatije. Najčešći simptomi UUTC-a su hematurija (75%) i bol u slabinama (30%). Ekskretorna urografija je još uvek metoda izbora u ispitivanju hematurije. Urinarna citologija pokazuje visoku specifičnost (preko 90%) ali nisku senzitivnost (ispod 50%). Fleksibilna ili rigidna ureteroskopija omogućava biopsiju i služi za potvrđivanje dijagnoze sa senzitivnošću preko 80% ali niskom specifićnošću oko 60%. Ove dijagnostičke procedure ne omogućavaju ranu dijagnostiku, i mogu da propuste UUTC. Međutim, bolje razumevanje molekularnih mehanizama uključenih u procese karcinogeneze i razvoja tumora donosi veliki broj potencijalnih molekularnih markera UUTC-a, sa potencijalnom prognostičkom i dijagnostičkom vrednošću. Ispitivanje molekularnih karakteristika urotelijalnih karcinoma je u toku, sa ciljem da se otkrije veza između genotipa tumora sa individualnim fenotipom i da se otkrije specifičan dijagnostički marker koji je udružen sa molekularnom biologijom tumora. Ako bi se ustanovio genetski profil sa rizikom, bilo bi moguće predvideti ćak i sprečiti razvoj urotelialnog karcinoma kod određenih pacijenata. Dalja israživanja su neophodna sa ciljem da se pronađe najbolji marker za ranu detekciju UUTC-a. Idealni UUTC test još uvek nije dostupan, te eventualni "zlatni standard" bi predstavljao multiple eseje koji analiziraju nukleinske kiseline i detektuju proteine. Pored toga, ovi testovi bi pružali kliničarima istovremeno informacije o prognozi i individualnom terapijskom pristupu.*

Ključne reči: *Karcinom gornjeg urinarnog trakta, biomarkeri, dijagnoza, prognoza*