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Clinical Relevance of Tumor Markers in Genitourinary Cancer Diagnosis and Treatment - a Literature Review

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Abstract:

Introduction and purpose: In recent years, the number of patients diagnosed with genitourinary cancers, including prostate cancer, kidney cancer, bladder cancer, and testicular cancer, has been increasing. Tumor markers—substances pathologically produced in the body during cancer development—ensure rapid diagnosis and subsequent treatment monitoring.

A brief description of the state of knowledge: In the case of prostate cancer, the primary tumor marker is prostate-specific antigen (PSA). It demonstrates high sensitivity but low specificity, and various parameters related to this marker allow accurate diagnosis or help avoid unnecessary biopsies. Markers associated with renal cell carcinoma (such as carbonic anhydrase IX and Ki67) have diagnostic potential but are not routinely used. Traditional testicular cancer markers (alpha-fetoprotein, human chorionic gonadotropin, lactate dehydrogenase) are routinely used to assess disease stage and prognosis. Bladder cancer markers (e.g., bladder tumor antigen, nuclear matrix protein 22) have varying levels of sensitivity and specificity, and unfortunately, none can replace cystoscopy.

Summary: Each of the diseases described has tumor markers of clinical significance; however, none of them is fully reliable, with the most common limitations being low specificity and the possibility of false-positive or false-negative results. Further research on new markers, including genetic and epigenetic ones, is needed to reduce treatment costs and enable more precise diagnosis of these diseases.

Key words: PSA; CA IX; VEGF; AFP; LDH;

Content

1. Introduction and Purpose

In recent years, the prevalence of genitourinary malignancies has risen noticeably. Among them, prostate, kidney, bladder, and testicular cancers are notably prominent in epidemiological statistics. A major clinical challenge lies in the fact that many of these cancers are asymptomatic during early stages, complicating detection and delaying therapeutic intervention. Tumor markers—biological substances secreted by cells in response to neoplastic processes—play a pivotal role in diagnostics and treatment monitoring.

Carefully selected biomarkers may facilitate earlier detection, support therapeutic decision-making, and assist in prognosis evaluation.

This review aims to explore both currently established and emerging tumor markers related to prostate, kidney, testicular, and bladder cancers. Additionally, it evaluates their clinical relevance, highlights their limitations, and suggests potential directions for future research and application.

The literature for this article was gathered through a structured review conducted on May 10th, 2025, using the PubMed and Google Scholar databases. Two independent reviewers (B.R. and W.K.) performed the search using terms such as "prostate cancer markers," "renal cell carcinoma markers," "bladder cancer markers," "testicular cancer markers," "PSA," and "NMP22." Supplementary references were included by reviewing the bibliographies of the selected articles.

2. Describtion of state of knowledge

2.1. Prostate Cancer (PCa)

Globally, prostate cancer (PCa) ranks as the second most frequently diagnosed malignancy in men, following only lung cancer. Data from 2018 indicate that 1,276,106 new prostate cancer cases were diagnosed, resulting in 358,989 deaths [1, 2]. Projections suggest that by 2040, the number of new diagnoses could approach 2.3 million annually, with mortality potentially increasing by 1.05% [1]. Higher incidence rates have been noted among men of African American and Caribbean descent [1, 3].

The dominant histopathological subtype of PCa is adenocarcinoma, accounting for over 95% of cases [3], although ductal carcinoma is also observed. Among men over 65, approximately six in ten cases of PCa are reported [3].

A key risk factor is family history. Men with a close relative affected by PCa face a 50% higher risk compared to those without such a background [4]. Additionally, inherited genetic mutations have been linked to increased susceptibility. Among the genetic markers implicated in PCa development are BRCA1/2, HOX family genes, ATM, and RNase L (HPC1, 1q22) [4]. BRCA mutations impair DNA repair mechanisms, thereby promoting oncogenesis. These genes serve as significant prognostic tools due to their association with multiple cancers, including PCa. For instance, BRCA1 mutation carriers aged 65 exhibit a 1.8 to 4.5-fold

increased PCa risk, while BRCA2 mutation carriers face a 2.5 to 8.6-fold increased risk compared to non-carriers [5, 6, 7].

Early-stage PCa is typically asymptomatic, emphasizing the need for reliable early detection methods. Measuring serum levels of prostate-specific antigen (PSA), a glycoprotein secreted by prostate epithelial cells, has become a key diagnostic strategy. PSA, primarily present in seminal fluid, is highly sensitive but not highly specific for PCa detection [8]. PSA concentrations above 4 ng/mL warrant further investigation. With PSA values between 4 and 10 ng/mL, the probability of PCa is around 25%, whereas levels exceeding 10 ng/mL raise this risk to over 50% [4]. However, because PSA is prostate-specific but not cancer-specific, elevated levels may also result from benign prostatic hyperplasia (BPH), prostatitis, or recent digital rectal examinations (DRE). Consequently, confirmation often requires a prostate biopsy [3, 4, 5].

Another clinically relevant parameter is PSA density (PSAD), especially in the "gray zone" of PSA values between 4–10 ng/mL. PSAD is calculated by dividing total PSA (tPSA) by prostate volume. A meta-analysis by Guo et al. found the area under the curve (AUC) for PSAD to be 0.78, with sensitivity and specificity of 79% and 57%, respectively, indicating PSAD's utility in cases with equivocal tPSA levels [9, 11].

Additionally, free PSA density (fPSAD) has been examined. Though less sensitive than tPSA, fPSA/tPSA, and PSAD for detecting PCa, fPSAD has shown higher specificity and diagnostic agreement [10]. Its improved accuracy makes it a promising diagnostic tool, especially due to its simplicity—it only requires fPSA measurement and prostate volume assessment. Notably, fPSAD has proven reliable even within the gray zone and offers potential to reduce unnecessary biopsies [10].

Several PSA-based parameters, including the fPSA/tPSA ratio, (fPSA/tPSA)/PSAD, PSAD, and the Prostate Health Index (PHI), have been introduced in clinical practice. Nonetheless, limitations in diagnostic performance and high costs hinder their widespread use [10]. Among these, fPSAD is particularly promising for its combination of accessibility and high specificity, making it clinically valuable in routine prostate cancer diagnostics.

2.2. Renal Cell Carcinoma (RCC)

Clear-cell renal cell carcinoma (ccRCC) constitutes approximately 80% of adult kidney cancers, making it the predominant RCC subtype [13]. Annually, more than 400,000 new

cases are diagnosed worldwide, and roughly 175,000 patients succumb to the disease. The highest incidence rates are seen in the United States and China [14, 15], with forecasts indicating a continued rise in occurrence in the coming years [14].

A significant clinical challenge with RCC is its silent progression—symptoms often do not appear until metastases develop, which substantially hampers early diagnosis and effective treatment [16, 17]. Numerous biomarkers have been proposed as potential prognostic indicators or therapeutic targets, yet none have gained routine application in diagnostics to date.

Among the most thoroughly studied markers is carbonic anhydrase IX (CA IX), a hypoxia-induced transmembrane protein expressed in multiple tumor types, including cervical, lung, and breast cancers, as well as RCC [18]. While high CA IX expression is linked to tumor aggressiveness and poor outcomes in many cancers [19], the opposite trend is noted in RCC. Several studies demonstrate that CA IX overexpression in RCC correlates with improved prognosis, extended survival (e.g., 67 vs. 22 months in Bui et al.'s study [20]), and reduced progression risk [20, 21]. Nonetheless, a minority of researchers dispute the prognostic value of CA IX [12].

Ki67, another marker under investigation, is a nuclear protein present in all proliferating cells [8, 10]. Its elevated expression in tumor tissues compared to normal ones suggests its utility as a prognostic biomarker and potential indicator of treatment response [23]. Higher Ki67 levels correlate with advanced RCC stage and metastatic disease, similar to its role in other cancers like breast cancer. Clinically, lower Ki67 levels indicate a more favorable prognosis [24, 25], though it is still viewed as a supplementary rather than definitive marker.

In ccRCC, activation of the vascular endothelial growth factor (VEGF) signaling pathway is commonly observed due to mutations in the VHL gene [26]. VEGF drives angiogenesis, facilitating tumor growth and spread [27]. Consequently, tyrosine kinase inhibitors (TKIs) targeting VEGF pathways are frequently used in treatment. Additionally, combining TKIs with immune checkpoint inhibitors—specifically targeting PD-1/PD-L1—has shown improved survival outcomes in clinical trials [27, 28].

Although none of the above markers have yet become standard diagnostic tools due to practical constraints, their relevance in prognosis and therapy continues to expand. Immune and molecular biomarkers are increasingly recognized for their role in personalizing treatment and guiding modern therapeutic strategies.

2.3. Testicular Cancer (TCa)

TCa accounts for approximately 1% of all adult malignancies and about 5% of urological cancers. The majority of cases are testicular germ cell tumors (TGCT), which are classified into seminomas and non-seminomas [29]. In Western countries, the incidence ranges from 3 to 11 new cases per 100,000 men annually. However, its occurrence increases significantly in specific age groups, particularly among young men aged 15 to 40, where it represents the most common malignancy [30]. The highest incidence rates are observed among European white male populations, and the number of cases has been steadily increasing over the past two to three decades. In 2020, the International Agency for Research on Cancer (IARC) reported 74,458 new cases of testicular cancer worldwide.

Currently, very few risk factors for testicular cancer have been identified. The only confirmed one is cryptorchidism, which increases the risk by 3.7 to 7.5 times compared to the general population [31]. Research in developmental biology has led to the identification of new biomarkers with clinical relevance for TGCT patients. Alpha-fetoprotein (AFP) and human chorionic gonadotropin (β-hCG) are secreted during embryogenesis and play crucial roles in normal development. Today, these serum markers, along with lactate dehydrogenase (LDH), constitute the only widely used circulating biomarkers for assessing disease stage and prognosis in TGCT patients. Despite their proven utility, their use has several limitations, highlighting the urgent need to develop and identify newer and more effective biomarkers [32, 33].

AFP is a single-chain glycoprotein with a half-life of 5–7 days, produced during embryonic development. Elevated AFP levels are observed in approximately 70% of patients with non-seminomatous testicular tumors, although it typically remains within normal limits in pure seminoma or choriocarcinoma cases [28, 34]. From a differential diagnostic standpoint, it is worth noting that elevated AFP levels may also occur in patients with lung, gastric, pancreatic, or hepatic cancers. Furthermore, non-malignant conditions such as drug-induced liver disease, autoimmune disorders, or infections may also lead to increased AFP levels [28].

LDH is an enzyme involved in the conversion of pyruvate to lactate. It is present in the kidneys and muscles, with a half-life of approximately 24 hours. LDH exists in five isoenzymes, among which LDH-1 is particularly associated with elevated levels in germ cell tumors. LDH-1 is linked to the short arm of chromosome 12, which may be amplified in these

tumors. Elevated LDH levels are seen in about 20% of low-malignancy germ cell tumors, and in advanced cases, this proportion may reach up to 60% [28].

β-hCG is a glycoprotein composed of two subunits: alpha and beta. The alpha subunit is similar to that of LH, FSH, and TSH, while the beta subunit is unique, enabling precise detection. Elevated β-hCG levels can be observed in various types of testicular tumors [28].

A major recent breakthrough in diagnostics is the discovery of circulating microRNAs from the miR371-3 cluster as novel tumor markers for TGCT. This biomarker meets all the key criteria for an ideal cancer marker, as proposed by Lange and Winfield. Its only notable limitation is low sensitivity in the case of teratomas, commonly referred to as the "teratoma gap" [35].

This innovative marker significantly outperforms traditional diagnostic methods due to its high sensitivity and specificity. It is predicted that miR371 may have five major clinical applications: (1) diagnosing testicular cancer, potentially reducing the need for biopsy or surgery in small tumors; (2) early detection of relapse during surveillance, possibly minimizing the number of imaging procedures and reducing costs; (3) diagnosing unclear retroperitoneal lymphadenopathy without invasive and expensive procedures; (4) rapid identification of non-responders to therapy, allowing for early treatment adjustments; and (5) evaluating residual masses after chemotherapy, which may reduce the need for surgery—though the teratoma gap must be considered. Altogether, this suggests that miR371 is poised to become a next-generation diagnostic tool for testicular cancer [35, 36].

2.4. Bladder Cancer (BC)

Bladder cancer affected nearly 600,000 individuals globally in 2020, and according to World Health Organization (WHO) projections, this number is expected to double by 2040 [38]. Men are more frequently affected than women (3–4:1), and over 90% of cases occur in individuals aged over 55. Numerous external factors contribute to the development of BC, including tobacco smoke, occupational exposure (particularly to organic chemicals), genetic predisposition, and parasitic infections such as *Schistosoma haematobium*—a relatively unique factor prevalent in North Africa [37, 38].

Two histological subtypes of BC are distinguished: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), each requiring different therapeutic

approaches [39]. Treatment of BC often involves multiple diagnostic and therapeutic procedures, which generate significant costs and negatively impact patients' quality of life.

The Food and Drug Administration (FDA) has approved several tumor markers that, despite limitations, can be useful throughout the treatment process—for example, by reducing the frequency of follow-up cystoscopies [40]. Currently, the only commonly used urinary marker is urine cytology, which is recommended as a complementary method to cystoscopic examination [41]. Its sensitivity is estimated at around 48%, and specificity at approximately 86%, though these values may vary depending on evaluator experience and tumor histology [42].

One FDA-approved urinary marker is the measurement of bladder tumor antigen (BTA), which detects human complement factor H-related proteins (hCFHrp). There are two variants: the qualitative BTA-Stat test (sensitivity 64%, specificity 77%) and the quantitative BTA-TRAK test (sensitivity 65%, specificity 74%) [43]. Hematuria, urinary stones, or infections may cause false-positive results, thus this test should not replace cystoscopy [44]. A meta-analysis by Guo et al. showed that urine cytology outperforms BTA-Stat in many predictive metrics (e.g., specificity, positive and negative likelihood ratios), although BTA-Stat demonstrates higher sensitivity [45].

Nuclear matrix protein 22 (NMP22) is a nuclear component naturally present in small quantities in healthy cells, involved in coordinating gene expression. Abnormal overexpression of NMP22 has been reported in various cancers, including colon, prostate, bladder, and breast cancer [46, 47]. Studies show that NMP22 has higher sensitivity (81.0–81.3%) and specificity (77–92%) in detecting transitional cell carcinoma compared to urine cytology and BTA-Stat [46, 48, 49]. However, it may still yield false-negative results, particularly in low-stage or low-grade tumors [46].

Additionally, Lau et al. demonstrated that patients who underwent TURBT (transurethral resection of bladder tumor) and had negative postoperative cystoscopy but a positive NMP22 result were at higher risk of cancer recurrence than those with a negative NMP22 result. Moreover, there was no significant association between NMP22 levels and overall survival [50].

UroVysion is a genetic test based on the FISH (fluorescence in situ hybridization) technique. It detects specific chromosomal abnormalities commonly found in BC, including aneuploidy

of chromosomes 3, 7, and 17, or loss of the 9p21 locus. The test uses exfoliated cells collected from urine samples [51].

A meta-analysis by Hajdinjak et al. showed that UroVysion has higher sensitivity than urine cytology (72% vs. 42%), though lower specificity (84% vs. 96%). Thus, both positive and negative results significantly influence the post-test probability of disease [52]. It is important to note that other conditions, such as prostate cancer or metastases to the urinary tract, may also lead to false-positive UroVysion results [53]. Therefore, test results should always be interpreted in conjunction with other clinical and diagnostic information.

3. Conclusions

Each of the discussed cancer types has tumor markers with proven clinical relevance; however, none can be considered fully reliable. The most common limitations include low effectiveness (e.g., PSA) or the possibility of false-positive/false-negative results (e.g., NMP22, BTA). Promising developments involving genetic and epigenetic markers offer potential for reducing the need for invasive procedures and supporting the implementation of personalized oncology. Many sources emphasize the importance of validating these markers in large-scale clinical trials and ensuring their effective integration into routine clinical practice.

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Authors' contribution

Conceptualization: BR and WK;

Methodology: BR and JMM;

Software: WK and JMM;

Check: KS, BR and AD;

Formal analysis: KS;

Investigation: BR and KS;

Resources: MJ and NK;

Data curation: MJ;

Writing - rough preparation: BR and WK;

Writing - review and editing: MJ, KS and JMM;

Visualization: MJ and WK;

Supervision: KS;

Project administration: BR;

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