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Title:

glance at the recent biomarkers in Genitourinary cancers

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Abstract :

Introduction

In recent years, the management of genitourinary cancers has changed substantially. Renal cell carcinoma, bladder urothelial carcinoma, and prostate adenocarcinoma are the most frequent genitourinary malignancies, and they represent a diverse group of cancers in terms of histology and therapeutic options. Due to a better understanding of their underlying molecular mechanisms and oncogenic drivers, all three malignancies have undergone paradigm shifts in their distinct treatment landscapes. Immunotherapies, particularly immune checkpoint inhibitors, are a new advancement that has acquired a lot of traction. Men's malignancies of the genitourinary system (GUS) are among the most common. Cancers of the prostate, bladder, and kidney are the first, fourth, and sixth most common cancers, respectively. Several recent genetic and molecular studies have provided new information concerning oncogenes and the growth of GU malignancies, such as bladder, prostate, and kidney cancers. These in-depth research have led to the discovery of new molecular categories based on genomic expression profiles, as well as potential diagnostic and therapeutic molecular targets.

This research aims to identify definition of Genitourinary cancers and Types of Genitourinary cancers (bladder cancer , kidney cancer , prostate cancer , identify of Emerging diagnostic biomarkers of Genitourinary cancers and methods of diagnosis and Recent therapeutic agents for Genitourinary cancers

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Introduction :

Malignancies of the genitourinary system (GU) are a diverse category of tumors that affect a specific anatomical and physiological function. The biochemical diversity of primary genitourinary cancers is astounding. The most prevalent histological subtypes within this group are renal cell carcinoma (RCC), urothelial carcinoma of the bladder, ureter, and renal pelvis (UC), and prostate adenocarcinoma (PC). There is an urgent and unmet need for new therapies in the world, with an annual morbidity of 225,000 patients and a mortality of approximately 56,000 patients from metastatic genitourinary cancers (Mei, M ,2013).

The genitourinary system refers to the reproductive and urinary systems as a group of organs. Malignancies of the genitourinary system (GUCs) are a diverse category of cancers that begin in these organs and disrupt their function. The most common types of GUCs include kidney and bladder cancers in both sexes, as well as prostate, testis, and penile cancers in men and cervical, ovarian, and uterine cancers in women. These malignancies, along with a few additional unidentified GUCs, account for 25% of all solid tumours, and each one is distinct, with its own set of indications and symptoms. (Zarrabi,2019) Surgical, pharmaceutical, and radiation management can successfully treat GUCs in the early stages, but these treatments have a limited or palliative effect in the later stages. GUC diagnosis and monitoring procedures now available are frequently invasive and have low sensitivity and specificity. Given the significant morbidity and mortality rates associated with GUCs, the development of new tumour biomarkers and novel therapies remains a pressing and unmet need.(Boguslawska,2019) The significant number of GUCs patients are typically discovered at an advanced stage due to a lack of sensitive prognostic biomarkers, and the 5-year survival rate remains far from ideal. Researchers have recently focused their efforts on developing novel tumour biomarkers linked with GUCs screening, diagnosis, prognosis, and therapy efficacy evaluation in order to enhance their survival rate. Due to the increasing prevalence of these tumours, it is clinically important and necessary to investigate accurate biomarkers that can

predict the prognosis of genitourinary system cancers. Smoking is a well-known modifiable risk factor for numerous malignancies, including GUC . (Bukowski,2011)

With the advent of novel biomarkers and clinical validation of new diagnostic tools, we are seeing a rapid change in diagnostic modalities. Furthermore, the quick approval of a number of novel drugs for each tumour type has resulted in a paradigm change in treatment guidelines. Overall survival (OS) and progression-free survival (PFS) have both improved.

Also Tumors of the genitourinary system (GUS) are among the most prevalent cancers in men. Prostate, bladder, and kidney cancers are the first, fourth, and sixth most prevalent cancers in, respectively. Several genetic and molecular investigations have recently revealed new information about the oncogenes is and progression of GU malignancies, including bladder, prostate, and kidney tumours. These in-depth studies have resulted in new molecular classifications based on genomic expression profiles, as well as the identification of prospective diagnostic and therapeutic molecular targets.(Mazzucchelli,2016)

With the emergence of novel biomarkers and clinical validation of new diagnostic tools, diagnostic modalities are rapidly evolving. Furthermore, with the quick approval of a number of novel drugs for each tumour type, there has been a paradigm change in treatment guidelines. Overall survival (OS) and progression-free survival (PFS) rates have increased, and the exceptional success of the new arsenal of immunotherapies and targeted medicines has been hailed as a "revolution" in the treatment of GU malignancies. When revised statistics are released, we expect the new survival data to be reflected in NCI SEER outcomes.(Vickers,2017)

Clinical trials have helped patients by allowing more treatment alternatives to be approved, but they have also added to the complexity of treatment regimens that clinicians must manage. Patients' treatment plans have gotten more diverse as more data supporting each agent has become available, but there have been less studies evaluating the best sequence or combination of medications. Many of the ongoing current trials are looking into both repurposed drugs for GU tumours that have shown promise in other cancer models as well as

novel molecules. We highlight significant developing therapeutic drugs and therapy techniques for common GU malignancies, such as UC, RCC, and PC .(Mottet,2017)

- **Types of Genitourinary :**

1- **Bladder cancer :**

Bladder cancer is the sixth most common cancer in the United States, accounting for over 16,000 deaths per year. In people 35 years and older, as well as those with irritative voiding symptoms, risk factors for bladder cancer, or gross hematuria at any age, asymptomatic hematuria should prompt assessment with cystoscopy, renal function testing, and upper urinary tract imaging. The bladder tumour can be definitively diagnosed, staged, and treated with transurethral resection. Transurethral resection is used to treat non-muscle-invasive illness, which is usually followed by intravesical bacille Calmette-Guérin or intravesical chemotherapy. Because of the greater chances of progression and recurrence, bladder cancer that has spread to the muscle layer is usually treated with radical cystectomy and neoadjuvant chemotherapy. The U.S. Preventive Services Task Force stated that current evidence is insufficient to assess the balance of benefits and hazards of screening asymptomatic persons for bladder cancer.(Malats,2015)

UC is the ninth most commonly diagnosed cancer worldwide, the 13th most prevalent cause of death, and the most common cancer of the gastrointestinal tract. Bladder cancer is a disease of the elderly, with a median age of diagnosis of 73 years. Because many patients are not candidates for current conventional treatment, the frailty and morbidity that typically afflict the senior population creates a barrier to successful disease management. Renal insufficiency, neuropathy, hearing loss, and heart disease are all common in this age range, resulting in suboptimal eastern cooperative oncology group performance. The distinction between localised muscle-invasive, muscle-invasive bladder cancer (MIBC), and metastatic disease in bladder UC can be made. MIBC has a high chance of spreading to other parts of

the body. For MIBC, the current standard of care is neoadjuvant platinum-based chemotherapy followed by radical cystectomy. The usual approach's OS rates are still below optimal, and complication rates are significant. Locally advanced inoperable or metastatic UC has few treatment choices, and these disease states have a poor prognosis. These patients had a median OS of 12–16 months in the past, even when they responded to platinum-based treatment. Furthermore, roughly 50% of MIBC patients are ineligible for platinum-based chemotherapy treatment. There were no approved post-platinum therapy drugs available until 2016, and second-line treatment alternatives after disease progression had a 10% response rate. Since 2017, we've seen a slew of pivotal trials that have resulted in the approval of innovative drugs.(Antoni,2017)

Immune checkpoint inhibitors (CPI) are being used as a first-line treatment for patients with metastases who are not candidates for platinum-based therapy or who are experiencing disease progression following platinum therapy. Nivolumab, pembrolizumab, avelumab, atezolizumab, and durvalumab are CPIs that can be used for post-platinum salvage therapy. The tyrosine kinase inhibitor erdafitinib (Balversa) was recently granted accelerated approval by the US Food and Drug Administration (FDA) for patients with locally advanced or metastatic UC who had FGFR2 or FGFR3 genetic abnormalities and have progressed on prior platinum-containing chemotherapy. We are now seeing the approval of a slew of new treatment alternatives, many of which are in the midst of promising clinical trials that will undoubtedly enhance survival rates.(Siegel Rebecca,2019)

Bladder cancer (BC) is the ninth most commonly diagnosed malignancy worldwide, with a fatality rate of thirteenth. One of the most prevalent GUCs, 58,59 BC, causes substantial death in the elderly population. 60 Unfortunately, the five-year survival rates for BC have not improved significantly in over thirty years. Urothelial cell carcinoma of the bladder (UCC) is a kind of cancer that affects the urinary tract. It is the most frequent kind of BC, accounting for 95% of all cases diagnosed. Several urine-based diagnostics for UCC have been

developed and tested in various groups, particularly older people, in recent years. The expression levels of nAChRs should be taken into account in urological practise. Cigarette smoke is a significant contributor to the development of BC. Yamamoto et al. showed that repeated injection of nicotine increased mRNA expression of nAChRs 1–7, 1–4, and muscarinic acetylcholine receptors (mAChRs) M1–M5 subtypes in the rat bladder. Previous research has shown that nicotine exacerbates bladder illness by activating nAChRs expressed in many bladder cells, although the exact processes are unknown. To see if nicotine causes bladder epithelial cell proliferation and to figure out which signalling pathway is regulated by nicotine. Their findings demonstrated that persons who are exposed to nicotine may be at risk for negative consequences such as the development of BC. (Sun,2020)

Risk Factors:

Male sex, older age, white race, occupational exposure to specific chemicals, pelvic radiation, usage of drugs such as cyclophosphamide, persistent bladder infection/irritation, personal or family history of bladder cancer, and cigarette smoking are all known risk factors for bladder cancer. Additional links have been discovered in studies involving diabetes, obesity, and the human papillomavirus. Pioglitazone (Actos) use for more than a year has been linked to a small increase in the risk of bladder cancer. It's also possible that eating a lot of processed red meat raises your risk.

The most common kind of bladder cancer is urothelial (transitional cell) carcinoma, which accounts for over 90% of cases. Squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and mixed histology tumours are among the nonurothelial bladder malignancies, with squamous cell and adenocarcinomas accounting for the majority of nonurothelial tumours. Although squamous cell carcinoma accounts for just a tiny percentage of bladder cancer cases in Western countries, it is the most frequent kind in schistosomiasis-endemic areas, accounting for up to 81 percent of cases.(Siegel Rebecca,2019)

Diagnosis : Cystoscopy, renal function testing, and imaging of the upper urinary system, preferably using computed tomography (CT) urography, are all used in the initial evaluation of a patient with suspected bladder cancer.

LABORATORY TESTS: All patients with bladder cancer should have their serum blood urea nitrogen and creatinine levels checked to see if they have renal impairment. A complete blood count and comprehensive metabolic panel, including alkaline phosphatase level and assessment of liver function, are recommended if metastatic illness is suspected.

Initial treatment for bladder cancer is determined by the pathologic extent of the illness at the time of TURBT and subsequent staging using the tumor-node-metastasis classification system. In malignancies with a higher risk of progression or recurrence, TURBT is usually followed with single-dose intravesical immunotherapy with bacille CalmetteGuérin (BCG) or intravesical chemotherapy. CT, or computed tomography, or magnetic resonance imaging, is frequently used to assess encroachment beyond the bladder. Because of the possibility of a post-TURBT perivesicular reaction, which might make interpretation challenging, imaging should be done before TURBT. Bladder cancers that penetrate the muscle are often treated with radical cystectomy with prolonged lymphadenectomy, followed by cisplatin-based neoadjuvant chemotherapy, due to the higher risk of progression and recurrence. 17,36 In certain patients, bladder preservation is an option, which is usually followed by chemotherapy and radiation.

Depending on the tumour and grade, recurrent non–muscle–invasive bladder cancer is treated with acombination of TURBT, adjuvant intravesical therapy, maintenance BCG immunotherapy, and/or cystectomy. For patients with initial ladder preservation who have persistent or recurring muscle-invasive bladder cancer, cystectomy is frequently advised. In patients with low-risk tumours, intravenous BCG immunotherapy may be tried, but if there is no response, cystectomy should be performed. When a recurrent or chronic disease is invasive, chemoradiotherapy or palliative TURBT, as well as supportive treatment, are advised.(Malats ,2015)

2- **kidney cancer :**

Kidney cancer is a disease that starts in the kidneys and spreads throughout the body. It occurs when healthy cells in one or both kidneys become malignant and expand out of control, resulting in a lump (called a tumor). The most frequent type of kidney cancer in adults is renal cell carcinoma (RCC). RCC commonly begins in the lining of renal tubules, which are small tubes in the kidney. RCC is most commonly seen in the kidney, but it can also migrate to other regions of the body, most commonly the bones, lungs, and brain. RCC tumours come in a variety of shapes and sizes. Some varieties spread quickly, while others are less inclined to do so. Clear-cell, chromophobe, and papillary RCC cancers are the most prevalent. Transitional cell carcinoma (TCC), Wilms tumour (most commonly detected in children), and renal sarcoma are some of the other kinds of kidney cancer.(Orth,2000)

Kidney cancer, also known as renal cancer, is a disease in which the cells in the kidneys become malignant and grow out of control. This malignancy accounts for 2–3% of all cancers in adults. Cigarette smoking has been shown in epidemiological studies to be an independent risk factor in the progression of kidney cancer, with smokers having double the risk of nonsmokers. 54 As a result, discovering novel tumour iomarkers in this smoking-related malignancy is still a pressing necessity. Renal cell carcinoma is a type of kidney cancer that begins in the lining membrane of the kidney tubules (RCC). RCC is a heterogeneous illness, with the vast majority of patients falling into one of two histological subtypes: clear cell RCC (ccRCC) and nonclear cell RCC (ncRCC) (nccRCC). 55 RCC is a frequent GUC, with over 320,000 individuals diagnosed each year and a global death toll of more than 140,000 persons. The role of nAChR in the development of kidney cancer was initially proposed.(Xu, K. Y., & Wu,2015)

the risk factors :

Clear-cell, chromophobe, and papillary RCC cancers are the most prevalent. Transitional cell carcinoma (TCC), Wilms tumour (most commonly detected in children), and renal sarcoma are some of the other kinds of kidney cancer:

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- Age and gender– kidney tumours are most frequent in adults over 60, and men are more likely than women to develop them. Factors related to your way of life
- Being overweight or obese, as well as smoking, are key risk factors. Cigarettes contain chemicals (carcinogens) that harm kidney cells' genes.
- Cystic kidney disease, dialysis, renal stones, high blood pressure (hypertension), past radiation, long-term use of nonsteroidal anti-inflammatory medicines, and hepatitis C infection are all medical conditions and therapies that can raise the risk of kidney cancer.
- Inherited kidney cancer syndromes, such as von Hippel-Lindau (VHL) syndrome, Birt-Hogg-Dubé syndrome, tuberous sclerosis, and hereditary papillary RCC (HPRCC), or a family history of kidney cancer.(Gong,,2016)

Diagnosis :

• Computed tomography (CT) scans create a full picture of the kidneys and abdomen by using x-rays (belly). It's possible to do them with or without a contrast dye. There is only a small amount of radiation used. A CT scan can typically reveal whether a tumour is malignant or has moved beyond the kidney.

• Magnetic resonance imaging (MRI) scans produce a detailed image of the kidneys and abdomen without exposing the patient to radiation. They can be performed with or without gadolinium, a contrast dye that should be avoided in persons who are on dialysis or have very low renal function. An MRI is more expensive than a CT scan, takes longer to complete, and the images may not be as clear.

• Ultrasound is a non-invasive imaging technique that employs sound waves to provide a comprehensive picture of the kidneys and abdomen. It could be helpful in determining if a kidney mass is a fluid-filled cyst or a solid tumour. This test is performed without the use of contrast dye.(Wu,2018)

3- **Prostate cancer :**

prostate cancer is the second most frequent cancer in males and the second highest cause of cancer mortality. A man's chance of developing PC is one in nine. The anatomic extent of the disease, histologic grade, and serum prostate-specific antigen (PSA) level all influence the treatment of newly diagnosed PC. Radiation therapy or radical prostatectomy are frequently used to treat localised PC. Biochemical recurrence occurs in 27–53 percent of patients, according to statistics. Androgen receptors (AR) are a key therapeutic target for PC because they play such an important part in its aetiology. For nearly a century, androgen deprivation therapy (ADT), whether surgical or pharmacological, has been the standard of care. Castrate-resistant prostate cancer (CRPC) is identified in patients with a high PSA level despite receiving sufficient ADT . After commencing ADT, the average duration for castrate resistance to appear is 19 months . The primary goal of treatment at this point is to delay the onset of metastases. Docetaxel, a well-known chemotherapeutic drug, is currently the standard of care treatment for CRPC. Despite the fact that chemotherapy works in advanced PC, the median survival time is still less than two years. Due to the inevitable development of resistance, research into new agents has continued apace. As a result, with the introduction of abiraterone, an androgen synthesis inhibitor, and enzalutamide, an androgen receptor antagonist, the standard of care for PC has swiftly changed in recent years. The STAMPEDE and LATITUDE studies were critical in determining the efficacy of abiraterone plus prednisone plus ADT as a first-line treatment for men with metastatic castrate-sensitive prostate cancer (mCSPC). Both trials showed significant improvements in PFS and OS.(Taitt,2018)

Enzalutamide was approved for metastatic CRPC before or after docetaxel after the AFFIRM and PREVAIL trials. As a result, the standard of care for advanced PC has dramatically evolved in the last year. While some drugs have had positive results, treatment resistance is an unavoidable reality for the majority of patients. As a result, combining and sequencing agents in a PC has become a difficulty. First-line therapy for mCRPC has been established, however data on which second- and third-line medicines are most effective is lacking. Without clear

data favouring any single regimen, researchers evaluated treatments in an attempt to clarify appropriate sequences. Predictive biomarkers such as homologous repair mutations, mismatch repair mutations, and AR splice variants are starting to emerge and will help personalise treatment. Finally, extensive discussions with patients and consideration of many factors (such as illness volume, symptoms, age, functional level, and cost) all aid in treatment design decision-making.

prostate cancer is the second most frequent malignancy in males and the second largest cause of cancer-related mortality. The anatomic extent of the illness, histologic grade, and serum prostate-specific antigen level all influence PCa treatment. Radiation therapy or radical prostatectomy are frequently used to treat localised PCa. Unfortunately, past research has shown that roughly half of PCa patients will experience recurrence. Observational studies have suggested that nAChR and PCa may be linked. However, the link between nAChR and the likelihood of having PCa is still being researched. The nAChR subunit 5 is involved in the proliferation and invasion of human PCa cells, making it an important component of the nAChR family. According to Magnon et al., autonomic nerve growth has a role in PCa start and propagation. The significance of the parasympathetic nervous system (PNS) in PCa development and progression was revealed in this work using animal models of PCa. The findings demonstrated that the PNS's cholinergic fibres are responsible for PCa cell invasion and metastasis through producing ACh. Given the potential for ACh to activate nAChRs, knowing the precise involvement of these receptors in PCa may aid in the development of nAChRs-based therapeutics to regulate the disturbed autonomic processes implicated in prostate tumour progression.(Håheim,2001)

Risk factors :

The cause of prostate cancer is unknown, however it is known that its incidence rises with age, from 10% in men in their fifties to 90% in men in their nineties. Because the condition does not affect men who have been castrated before puberty, male hormones (androgens) such as testosterone must also be present. One of the few well-established risk factors is family history. Men with a first-degree relative who has prostate cancer are twice as likely to develop

the disease. The risk of having the condition rises as the number of family members affected rises; men with two or three first-degree relatives who have the disease have a five to tenfold greater risk of developing it. The risk of having the condition rises as the number of family members affected rises; men with two or three first-degree relatives who have the disease have a five to tenfold greater risk of developing it. The prevalence of clinical prostate cancer varies by geographic area. The incidence is lowest among Asian men. African-Americans have the highest incidences, followed by Caucasians. Northern Europe has some of the highest rates. Despite the fact that African-Caribbean men have a high incidence in the United States and Europe, Africans living in Africa have lower prevalence. Poor recordkeeping, lack of access to care, and the fact that many men die of other conditions before reaching the age when prostate cancer is prominent may all contribute to the low recorded incidence. These findings show that external factors, such as a high-fat diet, sexual behaviour, alcohol use, and occupational exposure, influence the chance of progression from latent to clinical prostate cancer, though these risk factors are currently being investigated. The risk of dying from prostate cancer increases with a higher BMI and adult weight gain. .(Taitt,2018)

- **Emerging diagnostic biomarkers of Genitourinary cancers and methods of diagnosis :**

Urological malignancies account for 33% and 7% of all solid neoplasms in men and women, respectively, and are frequently linked to a decline in quality of life and specific cancer mortality. The importance of early detection in the treatment of malignant neoplasms cannot be overstated. Despite decades of work, urologic cancers remain difficult to diagnose and prognosticate early. In around 70% of cases, kidney cancer is discovered by chance during ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) scans performed for other reasons. Invasive diagnostic methods such as prostate biopsy and cystoscopy are used to diagnose prostate and bladder cancer.(Vogelzang,2012)

Recent advances in the science have revealed that these neoplasms recognise genetic changes caused by intrinsic and/or external stimuli as the primary driver of carcinogenesis. Despite

recent research advances, the pathways that cause to urogenital carcinogenesis, progression, and metastasis remain unknown. The development of new promising target therapies would benefit from speculative research of new molecular pathways to increase present knowledge of the carcinogenic process. Furthermore, the discovery of new biomarkers would be a significant step forward in the treatment of urological cancer, especially because molecular assays typically have higher diagnostic accuracy. Biomarkers may also be useful in the monitoring of treatments, such as immunotherapies for urogenital cancer.(Gottlieb,2016)

1- **Potential biomarkers for bladder cancer:**

Several proteins have been identified as possible biomarkers for BLCA applications. Previous investigations by independent groups identified apolipoprotein A1 (APOA1) as a promising biomarker for the diagnosis of BLCA, either alone or as part of a biomarker panel. ELISAs were used to validate APOA1 for the diagnosis of BLCA, with overall sensitivity and specificity of 94.6 and 92.0 percent, respectively, and an area under the curve (AUC) of 0.982, indicating its capacity to identify BLCA. The sensitivity and specificity of APOA1 for early-stage BLCA detection were 83.8 percent and 94.0 percent, respectively, and the AUC was 0.978.(Chen,2012) In a second investigation, 2-DE MS analysis revealed differential expression of APOA1 in urine from BLCA patients and normal controls, and APOA1 was confirmed for the diagnosis of BLCA by ELISA, with sensitivity and specificity of 89.2% and 84.6 percent, respectively. The diagnostic sensitivity was enhanced to 93.7 percent by combining cytology and APOA1 expression. Transgelin 2 (TAGLN2) is a new biomarker candidate that was recently discovered in the BLCA tissue proteome and found to be differently expressed in bladder tissue and urine specimens. Immunohistochemical investigations revealed that TAGLN2 expression in tumour tissues was nearly 30-fold higher than in neighbouring non-tumor tissue, and that TAGLN2 in tissue could identify BLCA with an AUC of 0.999.(Li, C., 2014) Two-dimensional difference gel electrophoresis (2D-DIGE) and MALDI-TOF–MS were used to identify Gc-globulin (Gc) in the urine of BLCA patients.

Urinary Gc, as measured by ELISA, had a sensitivity of 92.3 percent, a specificity of 83.0 percent, and an AUC of 0.964 in this investigation. With an AUC of 0.889, urinary Gc was also able to distinguish infiltrating urothelial cancer from BLCA. Identical outcomes were obtained by immunohistochemical and Western blot analysis of bladder tumor tissue .(Li, F.,2012)

2- **Potential biomarkers for kidney cancer :**

Bosso et al. used an automated sample preparation method to examine 29 controls and 39 renal cell carcinoma (RCC) patients for the detection of kidney cancer-specific MS signals utilising MALDI-TOF–MS and LC-ESI–MS/MS for the diagnosis of kidney cancer. A cluster of three MS signals (m/z = 1827/1914/1968) was able to distinguish patients from controls with a specificity and sensitivity of 100% and 95%, respectively, in this investigation. Using a combination of magnetic bead-based weak cation exchange chromatography and MALDI-TOF–MS, another study identified kidney cancer-specific proteins in a total of 162 serum samples. In the clear cell RCC (ccRCC) group, three potential peaks discovered from RNA-binding protein 6 (RBP6), tubulin beta chain (TUBB), and zinc finger protein 3 (ZFP3) were increased and tended to recover to healthy control levels after surgery.(Bosso,2008) This three-peptide panel detected ccRCC patients with an AUC of 0.81–0.83 in this investigation, with a mean sensitivity of 88.38 percent, a mean specificity of 91.67 percent, and a mean sensitivity of 88.38 percent. Frantzi et al. used urine samples from 40 RCC patients and 36 controls to validate a panel of 86 RCC-associated peptides on a large scale, achieving a sensitivity of 80%, a specificity of 87 percent, and an AUC of 0.92. They next tested specificity in 1077 control samples, which included age-matched normal controls (n = 218) and disease control patients with similar cancer types or renal illnesses (n = 859). The panel of 86 RCC-associated peptides was able to distinguish RCC from closely related cancer types as well as non-malignant renal and systemic illnesses, according to their findings. Jeremiah et al. recently used ELISA and Western blotting to evaluate urine AQP1 (aquaporin 1) and

PLIN2 (perilipin 2) in urine samples from 720 patients having normal abdominal computed tomography, 80 healthy controls, and 19 patients with pathologically diagnosed RCC.Their results validated the ability of a screening protocol using urinary AQP1 and PLIN2 to diagnose patients with occult RCC.

(Yang,2014)

3- **Potential biomarkers for prostate cancer:**

The prostate-specific antigen (PSA) test, which is used to identify prostate cancer (PCa), has helped to improve prostate cancer diagnosis. Ueda et al. used low-molecular-weight proteome profiling to find neuropeptide-Y (NPY) in plasma from prostate cancer patients. They created a revolutionary technology for low-molecular-weight proteome profiling called Quick Enrichment of Small Targets for Mass Spectrometry (QUEST–MS) and used targeted MRM–MS technology to validate screening results in an independent sample set (n = 110).(Catalona,1991) The combination of NPY and PSA has 81.5 percent sensitivity, 82.2 percent specificity, and an AUC of 0.88 for prostate cancer diagnosis. Another study employed an MS-based proteomic profiling technique to discriminate benign prostatic hyperplasia (BPH) from cancer utilising a combination of urine PSA and CD14. For the differential diagnosis of BPH and cancer, the combination of urine CD14 and PSA had a sensitivity of 81–94% and a specificity of 84–100% in this study. Autoantibodies against peroxiredoxin 6 (PRDX6) and annexin A11 (ANXA11) in the blood of prostate cancer patients were found by Ummanni et al. as prostate cancer classifiers. demonstrating that these two possible prostate cancer-related autoantibodies might be utilised to distinguish prostate cancer patients from healthy controls Each antibody's sensitivity was from 70% to 80%, while the combination of PRDX6 and ANXA11 antibodies had a sensitivity of 90% and a specificity of 100% for cancer diagnosis. The Gleason grading system is used in prostate cancer to determine the prognosis of patients based on the histologic appearance of a prostate biopsy. For the prediction of aggressive prostate cancer, the performance of novel proteomic biomarkers linked to the Gleason score is

included. Al-Ruwaili et al. (Ueda, K., 2013) used surface-enhanced laser desorption/ionization time-of-flight MS (SELDI-TOF–MS) to validate the peptide-signal panel in serum from low- and high-Gleason score PCa. With an AUC of 0.90, this peptide-signal panel can distinguish high-Gleason-score PCa. Fujita et al. also discovered an FABP5 protein in urine extracellular vesicles from PCa patients with a high Gleason score. FABP5 has a better diagnostic ability (AUC = 0.86) than FABP6 in distinguishing high-Gleason-score PCa from general PCa (AUC = 0.76). These biomarkers aid in the diagnosis of aggressive PCa and can be used to predict the prognosis of PCa patients.(Fujita,2017)

- **Recent therapeutic agents for Genitourinary cancers :**

1- **therapeutic agents of bladder cancer:**

- Emerging immunotherapy through checkpoint inhibition :

Long ago, UC was thought to be an immunogenic tumour. Indeed, its immunogenicity has been harnessed as a treatment strategy, and UC has one of the longest histories of immunotherapy responsiveness. Bacillus Calmette–Guérin has been used as a treatment for more than 40 years. Immune checkpoint blockade is the most promising area of new treatments for metastatic UC at the moment. The approved post-platinum salvage therapy CPIs (nivolumab, pembrolizumab, avelumab, atezolizumab, and durvalumab) had objective response rates (ORRs) ranging from 15% to 31%.(Rao,2019)

Both atezolizumab and pembrolizumab have been studied in patients who are receiving CPI as a first-line monotherapy for metastatic UC. Both atezolizumab and pembrolizumab showed clinically relevant effectiveness and objective responses in the phase II IMvigor210 trial and the phase II KEYNOTE-052 trial, respectively(Pignot,2019). Both medicines are currently being explored as monotherapies and in combination with chemotherapy in previously untreated patients with locally advanced unresectable or metastatic illness in phase III trials. The trials are identical in design, with PFS and OS as the major objectives. The IMvigor130 (NCT02807636) and KEYNOTE-361 (NCT02853305) studies for atezolizumab and pembrolizumab are presently underway, with highly expected results. The progress of these trials, however, may be confusing. According to preliminary findings, these medicines may be less successful than chemotherapy in some patients, and monotherapy should be reserved for those with high PD-L1 expression. In fact, participants in the CPI arm of the trials who had low PD-L1 levels had a lower survival rate than those who got cisplatin- or carboplatin-based chemotherapy.(Balar,2017)

- Emerging immunotherapy through cytokine modulation :

Alternative immunomodulation methods in UC have been investigated in addition to CPI. At this time, two cytokine-based agonists are being studied in metastatic UC. NKTR-214 is a new agent that is currently being studied in a phase I/II environment. NKTR-214 is a first-in-class CD122 selective agonist that acts as a pegylated recombinant interleukin-2 (IL-2) with cellular effects in the activation of CD8+ T and natural killer (NK) cells in the tumour microenvironment without the undesirable development of T regulatory (Treg) cells (Bentebibel,2019). The PIVOT-02 trial combines NKTR-214 with either nivolumab or ipilimumab/nivolumab therapy in a multi-cohort phase I trial. Patients with platinum-refractory metastatic UC who are having first-line immunotherapy are included in PIVOT-02 (NCT02983045). The objective responses were notable in preliminary results given at the 2019 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium. In efficacy-evaluable patients, the ORR was 48 percent, with 19 percent indicating a full response (CR). Immune-related RECIST showed a 52 percent ORR. Only 15% of patients had grade 3 treatment-related adverse events (TRAEs), and no patients had grade 4/5 TRAEs, indicating that the medication was well tolerated. Furthermore, after receiving combination therapy, 70% of patients who were PD-L1–negative prior to treatment became PD-L1–positive expressers. PD-L1 positivity was maintained in all PD-L1–positive patients . These findings are a significant step forward in immunotherapy treatment, as PD-L1 deficiency remains a barrier to optimum treatment for many patients.(Siefker-Radtke,2019) It provides as a proof-of-concept for new techniques to PD-L1 expression induction. The specific mechanism of PD-L1 modulation is unknown, although there was an increase in CD8+ T cells in patients who had an on-treatment biopsy compared to a baseline biopsy. These preliminary trial results have spurred the larger phase II PIVOT-10 study, which will evaluate NKTR-214 in combination with nivolumab in cisplatin-ineligible patients with low PD-L1 expression who have locally progressed or metastatic UC (NCT03785925). The phase I PROPEL trial is a different but comparable trial in premise to PIVOT-02 (NCT03138889). In patients with platinum-resistant mUC, PROPEL is testing atezolizumab in combination with NKTR-214 dose escalations. CYT107, a glycosylated recombinant IL-7 agent, is another cytokine agonist in the phase II stage of development.Platinum-resistant and cisplatin-ineligible mUC patients are being subject to treatment with intramuscular CYT107 with atezolizumab versus atezolizumab monotherapy (NCT03513952).(Balar,2019)

2- **therapeutic agents of kidney cancer :**

The type of treatment you receive is determined by the stage of kidney cancer you have, as well as your overall health, age, and other considerations. One or more of the following alternatives may be included in your treatment:

- The most frequent treatment for kidney cancer is surgery, which can cure most people with early stage cancer (stages 1, 2, and 3).
- Only the tumour or the portion of the kidney containing the tumour is removed, leaving as much of the kidney as feasible.
- The entire kidney is removed in a radical nephrectomy. The surrounding tissues and lymph nodes may also be removed if necessary.
- Thermal ablation burns or freezes the tumour to death. It's most commonly utilised for tiny tumours in those who don't qualify for nephrectomy surgery.
- If a tiny tumour is less than cm (1/2 inch), active surveillance is used. Small tumours usually grow slowly and aren't always cancerous. You'll need to monitor and test your system on a frequent basis.(Motzer,2011)

3- **therapeutic agents of prostate cancer :**

Prostate cancer treatment options are influenced by the stage of the disease and the preferences of the patient. It's critical for men to understand how treatment affects their physical appearance, sexual experience, sexual function, ejaculation, fertility, and urine function. Before beginning treatment, patients may need numerous meetings with doctors and expert nurses to discuss their disease state and treatment options. Men should be offered sperm storage, access to specialist erectile dysfunction and continence services, and psychosexual counselling where needed.(Chen,2003)

- **Conclusion :**

In the last few years, we've made significant progress in our knowledge of the molecular interactions that occur in tumour biology. To improve present methods for early diagnosis and therapy, the field of genitourinary oncology requires the convergence of data from basic science and clinical research. GUC cases have been on the rise, and over 33,000 people are expected to die each year as a result. With the rising incidence of GU malignancies, efforts have been made to improve the efficacy of current treatment options and to develop new diagnostic and therapeutic targets. However, these initiatives will need to be bolstered. As the burden of these diseases grows, so does the need for optimization and innovation. In males, 84 GUCs come from various types of cells found in the kidney, bladder, prostate, testis, and penis, whereas females get them from three primary gynecologic malignancies. Both male and female genitourinary tissues express nAChRs, which play a significant role in genitourinary tissue structure and function. Overall, 7nAChR, an emerging pharmaceutical target for a range of medical diseases, is expressed in the majority of GUC tissues, with varying consequences. This receptor found in GUCs holds a lot of promise, especially in light of recent breakthroughs. nAChR-based medicines may decrease disease development in GUCs, according to a growing body of research. There is presently no standard of care or systemic therapy for GUCs. As a result, nAChRs may be a valuable signature for managing GUCs, leading to a change in present alternatives. Nicotine is used to help people quit smoking and to treat a variety of ailments. The discipline has been transformed by important improvements in our understanding of GU cancer biology. The introduction of new drugs, notably immunotherapeutics, has had a significant impact on the area. The future of GU oncology is bright, and ongoing biomarker validation in conjunction with combination therapy will almost certainly improve the efficacy of our treatments.

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