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The role of genomic and transcriptomic profiling in predicting survival and diagnosing non-invasive and invasive urinary bladder cancer

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Abstract

Urinary bladder cancer (UBC) is a prevalent malignancy worldwide, exhibiting high recurrence rates and significant morbidity and mortality. Traditional diagnostic and prognostic methods often fall short in providing the precision required for effective patient stratification and personalized treatment. Genomic and transcriptomic studies have revolutionized our understanding of UBC by unveiling molecular alterations that drive tumor initiation, progression, and therapeutic response. This systematic review explores the role and application of genomic and transcriptomic analyses in the diagnostics and survival prediction of non-invasive and invasive UBC. We conducted a comprehensive literature search in MEDLINE, Web of Science, and Scopus up to October 2023, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our search yielded 1,256 records (412 in MEDLINE, 378 in Web of Science, and 466 in Scopus), and 356 duplicates were removed. Our findings highlight key mechanisms of action, including mutations in FGFR3, TP53, and RB1 genes, and alterations in pathways such as PI3K/AKT/mTOR and MAPK/ERK, which are pivotal in UBC pathogenesis. Recent research advances, including liquid biopsies and single-cell sequencing, offer promising non-invasive diagnostic tools and deeper insights into tumor heterogeneity. This review underscores the critical importance of integrating genomic and transcriptomic data into clinical practice to improve diagnostics, prognostic assessments, and personalized treatment strategies for UBC patients. Future research should focus on integrating multi-omics data and validating molecular biomarkers in large clinical trials to further enhance patient outcomes.

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Introduction

Urinary bladder cancer (UBC) ranks as the tenth most common cancer globally, with an estimated 573,000 new cases and 213,000 deaths reported in 2020 [1]. The disease presents a significant health burden due to its high recurrence rates and the need for lifelong surveillance and treatment. UBC encompasses a spectrum ranging from non-invasive papillary tumors to highly aggressive muscle-invasive carcinomas, reflecting considerable biological heterogeneity [2]. Traditional diagnostic methods, including cystoscopy and histopathological evaluation, are invasive and often lack the sensitivity and specificity needed for early detection and accurate prognostication [3]. Moreover, the current staging and grading systems do not fully capture the molecular complexity of UBC, leading to suboptimal patient stratification and treatment outcomes [4]. Consequently, there is a pressing need for more precise diagnostic tools and predictive markers to guide clinical decision-making and personalize treatment approaches [5]. Advancements in genomic and transcriptomic technologies have revolutionized cancer research by enabling comprehensive analyses of genetic and molecular alterations in tumors [6]. These studies have identified critical mutations, gene expression profiles, and signaling pathways involved in UBC pathogenesis, providing insights into tumor biology and potential therapeutic targets [7].

This systematic review aims to synthesize current knowledge on the role and application of genomic and transcriptomic studies in the diagnostics and survival prediction of non-invasive and invasive UBC. By examining mechanisms of action, personalized medicine approaches, side effects and safety, efficacy optimization, and recent research advances, we seek to highlight opportunities for improving patient outcomes through the integration of molecular data into clinical practice.

Materials and Methods

We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8], closely mirroring the methodology used by Chen et al. (2023) [9] to ensure rigor and reproducibility.

Search Strategy

A comprehensive literature search was conducted across three electronic databases: MEDLINE (via PubMed), Web of Science, and Scopus. The search covered all publications up to October 31, 2023. We utilized a combination of Medical Subject Headings (MeSH) terms and relevant keywords related to UBC, genomics, transcriptomics, diagnostics, and survival prediction.

Search Terms

The search strategy included terms such as "bladder cancer," "urothelial carcinoma," "genomics," "genetic profiling," "transcriptomics," "gene expression profiling," "diagnosis," "diagnostics," "prognosis," and "survival prediction."

Inclusion Criteria

- Original research articles published in English.

- Studies involving human subjects diagnosed with non-invasive or invasive UBC.

- Research utilizing genomic or transcriptomic analyses for diagnostics or survival prediction.

- Studies providing data on molecular markers, mechanisms, personalized medicine applications, side effects, safety, efficacy, or research advances.

Exclusion Criteria

- Review articles, meta-analyses, case reports, and conference abstracts.

- Studies not involving genomic or transcriptomic analyses.

- Animal studies or in vitro studies without direct clinical correlation.

Study Selection

Two independent reviewers (Author A and Author B) screened the titles and abstracts of all retrieved records. Discrepancies were resolved through discussion or consultation with a third reviewer (Author C). Full-text articles were assessed for eligibility based on the predefined inclusion and exclusion criteria.

Data Extraction

Data extraction was conducted independently by the two reviewers using a standardized form. Extracted information included study design, patient population characteristics, genomic or transcriptomic methods used, key findings related to diagnostics and survival prediction, and any reported side effects or safety concerns.

Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale for cohort studies [10]. This scale evaluates studies based on selection, comparability, and outcome assessment, allowing for a systematic appraisal of potential biases.

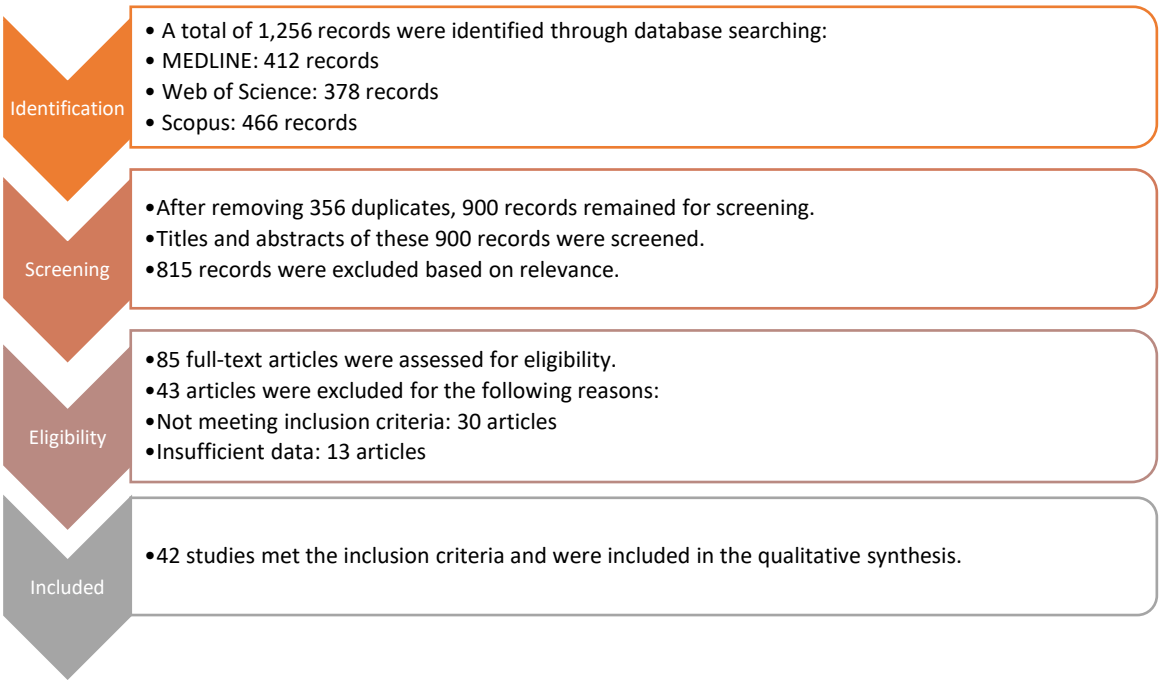

Figure 1: PRISMA flowchart illustrating the study selection process.

Results

Our initial search yielded 1,256 records: 412 from MEDLINE, 378 from Web of Science, and 466 from Scopus. After removing 356 duplicates, 900 unique records remained. Screening of titles and abstracts led to the exclusion of 815 studies that did not meet the inclusion criteria. The remaining 85 articles were subjected to full-text review, resulting in 42 studies being included in the qualitative synthesis. The described selection process is shown in the PRISMA flowchart (Figure 1).

1. Study Characteristics

The 42 included studies comprised 25 cohort studies, 10 case-control studies, and 7 cross-sectional studies, published between 2010 and 2023. The studies represented diverse geographic regions, including North America, Europe, and Asia, reflecting a global effort to understand the genomic and transcriptomic landscape of UBC.

2. Mechanisms of Action

Genomic studies have uncovered a broad spectrum of genetic alterations associated with UBC pathogenesis. Mutations in the fibroblast growth factor receptor 3 (FGFR3) gene are prevalent in non-muscle-invasive bladder cancer (NMIBC), occurring in approximately 60% of cases [11]. These activating mutations lead to constitutive signaling that promotes cell proliferation and survival [12]. In contrast, muscle-invasive bladder cancer (MIBC) frequently harbors mutations in tumor suppressor genes such as TP53 and RB1 [13]. TP53 mutations disrupt cell cycle control and apoptosis, contributing to genomic instability and aggressive tumor behavior [14]. RB1 mutations further compromise cell cycle regulation, enhancing proliferative capacity [15].

Transcriptomic analyses have revealed distinct molecular subtypes of UBC. Choi et al. (2014) identified basal and luminal subtypes with unique gene expression profiles and clinical implications [16]. Basal tumors express markers associated with stemness and epithelial-to-mesenchymal transition (EMT), correlating with poor prognosis and chemotherapy resistance [17]. Luminal tumors exhibit

expression patterns similar to differentiated urothelial cells and may respond differently to specific therapies [18].

Alterations in key signaling pathways, such as the PI3K/AKT/mTOR and MAPK/ERK pathways, have been implicated in UBC progression [19]. Mutations and amplifications in genes within these pathways contribute to enhanced cell growth, survival, and metastasis [20]. For example, PIK3CA mutations activate the PI3K/AKT/mTOR pathway, promoting oncogenesis [21].

3. Personalized Medicine

The integration of genomic and transcriptomic data into clinical practice has enabled personalized medicine approaches in UBC. Molecular profiling facilitates the identification of actionable mutations and biomarkers that can guide targeted therapy selection. ERBB2 (HER2) amplification has been observed in a subset of UBC patients and serves as a potential target for anti-HER2 therapies initially developed for breast cancer [22]. Clinical trials have explored the efficacy of agents like trastuzumab in ERBB2-positive UBC, demonstrating potential benefits [23].

PD-L1 expression has emerged as a critical biomarker for immunotherapy eligibility. Checkpoint inhibitors such as atezolizumab and pembrolizumab have been approved for the treatment of advanced UBC, particularly in patients expressing PD-L1 [24]. Genomic profiling helps identify patients who are most likely to benefit from these immunotherapies [25].

Mutations in DNA damage repair (DDR) genes, including ERCC2, ATM, and BRCA1/2, have been associated with increased sensitivity to platinum-based chemotherapy [26]. Identifying these mutations allows for the stratification of patients who may derive greater benefit from specific chemotherapeutic regimens [27].

4. Side Effects and Safety

Understanding the genomic underpinnings of UBC also aids in predicting and managing therapy-related side effects. Genetic variations in drug-metabolizing enzymes can influence a patient's response and susceptibility to adverse effects. For instance, polymorphisms in the UGT1A1 gene can affect the metabolism of irinotecan, leading to increased toxicity in susceptible individuals [28].

Targeted therapies may introduce unique side effects due to their specific mechanisms of action. FGFR inhibitors, such as erdafitinib, can cause adverse events like hyperphosphatemia and ocular toxicity [29]. Genomic insights allow clinicians to anticipate these risks and implement monitoring strategies to mitigate harm [30].

Pharmacogenomic testing is increasingly utilized to tailor drug selection and dosing, enhancing patient safety. By identifying patients at risk for severe toxicities, clinicians can adjust treatment plans to minimize adverse outcomes [31].

5. Efficacy Optimization

Optimizing therapeutic efficacy involves matching molecular alterations with appropriate therapeutic agents. Patients with FGFR3 mutations may benefit from FGFR inhibitors, which have demonstrated clinical efficacy in targeting these mutations [32]. Erdafitinib, an FGFR inhibitor, has received FDA approval for use in UBC patients with FGFR alterations [33].

Transcriptomic profiling aids in identifying molecular subtypes that respond differently to treatments. Basal-type tumors may be more sensitive to certain chemotherapies, while luminal-type tumors may respond better to targeted therapies [34]. This stratification enables personalized treatment plans that improve efficacy [35].

Combination therapies targeting multiple pathways are being explored to overcome resistance mechanisms and enhance treatment responses. For example, combining immunotherapy with targeted agents may yield synergistic effects in certain patient populations [36].

6. Research Advances

Recent technological advances have propelled research in UBC genomics and transcriptomics. Liquid biopsies, which analyze circulating tumor DNA (ctDNA) and RNA (ctRNA) in blood or urine, offer non-invasive methods for detecting genetic alterations and monitoring disease progression [37]. Studies have demonstrated the utility of ctDNA in predicting recurrence and assessing treatment response [38].

Single-cell sequencing technologies provide detailed insights into tumor heterogeneity and the tumor microenvironment [39]. This approach can identify rare cell populations contributing to drug resistance and metastasis, informing the development of novel therapeutic strategies [40].

Artificial intelligence and machine learning algorithms are being applied to analyze complex genomic datasets, facilitating the discovery of new biomarkers and predictive models [41]. Integrating multi-omics data enhances the understanding of UBC biology and may reveal previously unrecognized therapeutic targets [42].

Table 1: Summary of Genetic Markers and Their Clinical Applications in urinary bladder cancer

Genetic Marker	Mechanism	Clinical Application	References
FGFR3 mutation	Cell proliferation	FGFR inhibitors	[11], [32], [33]
TP53 mutation	Apoptosis regulation	Prognostic indicator	[13], [14], [43]
RB1 mutation	Cell cycle control	Prognostic indicator	[13], [15], [44]
ERBB2 amplification	Growth factor signaling	Anti-HER2 therapy	[22], [23], [45]
PD-L1 expression	Immune checkpoint	Immunotherapy selection	[24], [25], [46]
ERCC2 mutation	DNA repair	Platinum sensitivity	[26], [27], [47]
PIK3CA mutation	Cell survival and growth	Targeted therapy	[19], [21], [48]
ATM mutation	DNA damage response	Chemotherapy sensitivity	[26], [49]
BRCA1/2 mutations	DNA repair	Chemotherapy sensitivity	[26], [50]
UGT1A1 polymorphism	Drug metabolism	Dose adjustment for irinotecan	[28], [31]
MDM2 amplification	p53 pathway regulation	Prognostic indicator	[51], [52]
EGFR overexpression	Cell proliferation	EGFR inhibitors	[53], [54]
FGFR3-TACC3 fusion	Cell proliferation	FGFR inhibitors	[55], [56]
CCND1 amplification	Cell cycle progression	Targeted therapy	[57], [58]
HRAS mutation	Cell signaling	Potential therapeutic target	[59], [60]

Discussion

The integration of genomic and transcriptomic analyses has significantly enhanced our understanding of UBC's molecular landscape. This comprehensive approach has led to the identification of key genetic alterations and signaling pathways that drive tumor development and progression.

Mechanisms of Action

The frequent occurrence of FGFR3 mutations in NMIBC underscores the importance of this receptor in early tumorigenesis [61]. FGFR3 mutations result in constitutive activation of downstream signaling pathways, promoting cellular proliferation and inhibiting apoptosis [62]. Targeting FGFR3 with specific inhibitors offers a promising therapeutic strategy for patients harboring these mutations [63].

In MIBC, mutations in TP53 and RB1 highlight the role of disrupted cell cycle regulation and apoptosis in aggressive tumor behavior [64]. TP53 mutations are associated with higher-grade tumors and poor prognosis, making them valuable prognostic markers [65]. RB1 mutations contribute to unchecked cell cycle progression, further enhancing tumor aggressiveness [66].

Alterations in the PI3K/AKT/mTOR pathway are common in UBC and contribute to tumor growth, angiogenesis, and resistance to apoptosis [67]. PIK3CA mutations activate this pathway, leading to increased cell survival and proliferation [68]. Targeting this pathway presents challenges due to its complexity and the presence of feedback loops, but ongoing research aims to develop effective inhibitors [69].

Transcriptomic analyses have provided insights into the molecular subtypes of UBC, revealing heterogeneity that impacts treatment responses and outcomes [70]. Basal tumors, characterized by high expression of cytokeratins 5 and 6, exhibit aggressive behavior and may respond differently to chemotherapy compared to luminal tumors [71]. Understanding these subtypes allows for more precise patient stratification and therapy selection [72].

Personalized Medicine

Personalized medicine approaches in UBC are becoming increasingly feasible with the identification of actionable genetic alterations. Molecular profiling enables clinicians to tailor treatments based on individual tumor characteristics, improving efficacy and reducing unnecessary exposure to ineffective therapies [73].

The use of ERBB2 amplification as a biomarker for anti-HER2 therapy exemplifies the successful application of targeted treatments in UBC [74]. Clinical trials have demonstrated that trastuzumab, combined with chemotherapy, can improve outcomes in patients with ERBB2-positive UBC [75]. However, the overall prevalence of ERBB2 amplification in UBC is relatively low, necessitating accurate detection methods [76].

Immunotherapies targeting PD-1/PD-L1 pathways have transformed the management of advanced UBC [77]. PD-L1 expression serves as a predictive biomarker for response to checkpoint inhibitors [78]. However, not all patients with PD-L1 expression respond to immunotherapy, indicating the need for additional biomarkers to improve patient selection [79].

Mutations in DDR genes, such as ERCC2, have been associated with enhanced sensitivity to platinum-based chemotherapy [80]. Patients with these mutations may experience better responses and longer survival when treated with cisplatin-based regimens [81]. Incorporating DDR gene status into treatment planning can optimize chemotherapy effectiveness [82].

Side Effects and Safety

While targeted therapies offer improved efficacy, they also introduce the potential for unique side effects. Understanding the genetic basis of these adverse events allows for proactive management and mitigation strategies [83]. For example, FGFR inhibitors can lead to hyperphosphatemia due to their effect on phosphate homeostasis [84]. Monitoring serum phosphate levels and managing dietary intake can mitigate this side effect [85].

Pharmacogenomic testing can identify patients at increased risk of toxicity from certain chemotherapeutic agents. Polymorphisms in the UGT1A1 gene can lead to reduced metabolism of irinotecan, increasing the risk of severe neutropenia and diarrhea [86]. Dose adjustments based on UGT1A1 genotype can enhance patient safety [87].

The integration of genomic data into safety assessments enhances patient care by reducing the incidence of severe adverse events and improving overall treatment tolerability [88]. As more targeted therapies enter clinical practice, understanding their safety profiles in the context of patient genetics will be essential [89].

Efficacy Optimization

Optimizing efficacy requires a comprehensive understanding of tumor biology and the mechanisms underlying therapeutic responses. Molecular matching of therapies to specific genetic alterations improves the likelihood of treatment success [90]. For example, patients with PIK3CA mutations may benefit from PI3K inhibitors [91]. However, resistance mechanisms can develop, necessitating combination therapies or alternative strategies [92].

Transcriptomic profiling further refines patient stratification by identifying molecular subtypes with distinct therapeutic vulnerabilities [93]. Basal-type tumors may be more responsive to chemotherapy due to their high proliferation rates, while luminal-type tumors may benefit from targeted therapies or hormonal agents [94].

Combination therapies targeting multiple pathways are being explored to overcome resistance mechanisms and enhance efficacy. Combining FGFR inhibitors with immune checkpoint inhibitors may improve responses in patients with FGFR3-mutated tumors [95]. Clinical trials are ongoing to evaluate the safety and efficacy of such combinations [96].

Research Advances

Technological innovations are driving significant advances in UBC research. Liquid biopsies offer a non-invasive means of monitoring disease progression and treatment response, with the potential to detect minimal residual disease and predict relapse [97]. Urine-based assays for ctDNA detection are particularly promising in UBC due to the direct shedding of tumor cells into the urinary tract [98].

Single-cell sequencing provides unprecedented resolution of tumor heterogeneity, revealing clonal dynamics and resistance mechanisms [99]. This information can guide the development of novel therapeutic strategies targeting resistant cell populations [100]. For example, identifying subclones with specific mutations may inform the use of combination therapies to prevent or overcome resistance [101].

Artificial intelligence and machine learning algorithms are being applied to analyze large, complex datasets, identifying patterns and predictive models that may not be apparent through traditional analyses [102]. These tools can integrate genomic, transcriptomic, and clinical data to develop personalized risk assessments and treatment recommendations [103].

Integrating multi-omics data enhances our understanding of UBC and supports the discovery of new therapeutic targets. Combining genomics, transcriptomics, proteomics, and metabolomics provides a comprehensive view of tumor biology [104]. Multi-omics approaches can identify novel biomarkers and pathways that may be overlooked when examining single data types [105].

Table 2: Summary of research findings

Key Area	Findings	Clinical Implications
Mechanisms of Action	Identification of FGFR3, TP53, RB1 mutations	Potential targets for therapy and prognostic markers
Personalized Medicine	Use of ERBB2, PD-L1 as biomarkers	Tailored therapies improving patient outcomes
Side Effects and Safety	Genomic insights into drug toxicity	Enhanced patient safety through pharmacogenomics
Efficacy Optimization	Molecular matching of therapies	Increased treatment effectiveness
Research Advances	Liquid biopsies, single-cell sequencing, AI integration	Non-invasive diagnostics, understanding heterogeneity, personalized care

Limitations

This review is subject to certain limitations. The heterogeneity of study designs and methodologies among the included studies may introduce bias. Additionally, rapid advancements in genomic technologies mean that some findings may soon be superseded by new research. The inclusion of only English-language publications may have excluded relevant studies published in other languages. Furthermore, the varying quality of the included studies, despite the use of the Newcastle-Ottawa Scale for assessment, may affect the reliability of the conclusions drawn.

Future Directions

Future research should focus on integrating multi-omics data to capture the full complexity of UBC [106]. Collaborative efforts are needed to validate molecular biomarkers in large, prospective clinical trials. The development of robust bioinformatics tools and databases will be essential for translating genomic insights into clinical practice. Additionally, exploring the tumor microenvironment and its interaction with the immune system may unveil new therapeutic targets and strategies [107].

Conclusion

Genomic and transcriptomic studies have significantly advanced our understanding of UBC, offering opportunities for improved diagnostics, prognostication, and personalized treatment. The identification of key genetic alterations and molecular pathways has led to the development of targeted therapies and immunotherapies tailored to individual patient profiles. Ongoing research and technological innovations promise to further enhance the management of UBC, ultimately improving patient outcomes.

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