Review Article on Update on Molecular Classification and Individualized Treatments of Genitourinary Tumors

A narrative review of individualized treatments of genitourinary tumors: is the future brighter with molecular evaluations?

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Abstract: Few molecular prognostic and predictive biomarkers have been identified so far in genitourinary tumors. We started from a literature search to explore the status of the art of molecular pathology tests as diagnostic, prognostic, predictive biomarkers in genitourinary cancers. Next generation sequencing approaches now provide mind-changing information in the fields of kidney cancer diagnosis, predictive oncology of urothelial cancer, understanding the causes of testicular and penile cancer, and the comprehension of the drivers of prostate cancer progression beyond androgen regulation. The classification of kidney cancer will be based soon on molecular changes. The causes of non-HPV related penile cancer are largely unknown. The emerging high incidence of testicular cancer could be explained only on the basis of molecular changes. The response to novel therapeutic agents in prostatic and urothelial cancer will require thorough molecular tumor characterization. The hereditary risk of patients with early onset prostate cancer and their potential treatment with targeted therapy requires germline and somatic genetic assays. The implementation of effective biomarkers for the response to immune check-point inhibitors in genitourinary cancer is based on the assessment of inflammatory expression profiles and the tumor mutational burden. This review deals with the current tests and provides a tentative foresee of the future molecular biomarkers of genitourinary cancer.

Keywords: Molecular pathology; precision medicine; genitourinary tumors

Submitted Aug 18, 2020. Accepted for publication Oct 19, 2020.
doi: 10.21037/tau-20-1185
View this article at: http://dx.doi.org/10.21037/tau-20-1185

Background

Personalized medicine is the frontier of oncological treatments in this new century. Molecular characterization is currently mandatory in most human malignancies for precise diagnosis and to predict response to targeted biological drugs. Genitourinary cancers are particular in the landscape of solid tumors since few molecular prognostic and predictive biomarkers have been identified so far in these tumor types. In fact, the diagnosis of prostate cancer still largely relies on histology, while the therapeutic advances in lethal prostate cancer still mainly involve hormone therapy and in a small proportion of cases drugs targeting single germline genetic alterations. The molecular classification of urothelial cancer has been a major advancement in understanding the biology of this cancer type. However, the hands-on application of this molecular classification is still under-recognized by most pathologists and the predictive significance of molecular biomarkers in cancer therapy is poorly understood except for immunotherapy. Kidney cancer represents the most rapidly evolving field among solid tumors in terms of change in subtype classification. The next classification of the world health organization will encounter a large number

of additional kidney cancer types based on molecular distinctive features as it happened to the previous edition in 2016. This improved understanding of kidney tumors with different molecular traits and shared histological features will likely impact the diagnostic and surgical approach to kidney lesions but will not probably change the therapeutic strategy of advanced/metastatic cases. Testicular cancer is facing a new epidemiological outbreak and a new biological classification is linking similar histology to a different carcinogenetic pathway and age of occurrence. Molecular advances in testicular cancer might therefore affect mainly diagnosis since oncologic therapy is standardized and associated with good clinical responses in most metastatic cases. Finally, penile cancer is a niche in both pathology and oncology and it has been mainly related to human papilloma virus (HPV) infections. The main molecular interest is focusing on non-HPV related tumors and the complex relations between cancer and the associated inflammatory microenvironment.

The rationale of this review is to start from a literature search and explore the status of the art of the impact of molecular pathology tests as diagnostic, prognostic, predictive biomarkers in genitourinary cancers. The main objective is to foresee the benefits that molecular tests will bring to the patients harboring these tumor types. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1185).

Methods

We performed a review of PubMed/Medline in June 2020 for the previous ten years using the following search items: genitourinary tumors and molecular classification (286 results); genitourinary tumors and molecular diagnosis (1,042 results) genitourinary tumors and molecular biomarkers (1,232 results); genitourinary tumors and therapy biomarkers (3,127 results). We applied a selection diagram to the results according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (1). After further filtering to exclude: (I) experimental studies in animals; (II) studies on gynecological cancers; (III) generic studies on solid tumors including genitourinary cancers; (IV) review articles; (V) case reports, 383 publications were selected for inclusion in this analysis. The most significant reports have been utilized as the base for the commentary of the following two topics: molecular classification and diagnosis of genitourinary tumors; molecular prognostic and predictive biomarkers in genitourinary tumors.

Molecular classification and diagnosis of genitourinary tumors

The classification of kidney neoplasms has changed in the last 10 years to include several new entities, previously underestimated, characterized by similar features at H&E staining but with totally different genetic basis and clinical behavior. The recognition of these new entities that started with the meeting of the International Society of Uropathology in Vancouver in 2009 and has been recognized in the WHO classification of 2016 (2,3).

The diagnosis of several of these new entities derived from a better molecular tumor characterization. For instance, the molecular distinctive trait of the clear cell papillary from conventional clear cell cancer is the absence of *VHL* alterations and now this histotype is commonly diagnosed on the basis of the $CK7^{+}$racemase^{-}CA-IX^{-} immunohistochemical algorithm (4,5). The diagnosis of other renal cell tumors with papillary morphology such as the tumors associated with the succinate dehydrogenase (*SDHB*) or the fumarate hydratase (*FH*) deficiency has been possible after the clarification of the role of the Krebs cycle genes alterations in renal cell tumors and it is easily possible with specific immunohistochemical stains (6,7). X;11 and 6;11 translocation tumors associated with the MIT family genes (*TFE3* and *TFEB*) fusions represent a well-defined group of pediatric and adult kidney tumors whose diagnostic final confirmation is made possible by break-apart FISH or next generation sequencing methods (8,9). The number of new tumor kidney entities is steadily growing and will be likely recognized by the new WHO classification of genitourinary tumors. Among these new entities the tumors associated with alterations of the TSC-mTOR pathway are particularly relevant (10). The so-called eosinophilic solid and cystic renal cell cancer is part of this tumor group and it is characterized by mutations in the *TSC2* gene, distinctive immunoreactivity for cytokeratin 20, and favorable clinical behavior (11). Besides, several other renal tumor types are encountered in patients harboring alterations of the tuberous sclerosis complex. For instance, renal cancer with clear cell morphology and prominent muscle stroma or high-grade tumors with eosinophilic and chromophobe-like features often display mutations in *TSC1*, *TSC2* and *mTOR* genes (12,13). The increasing use of next generation sequencing panels in solid tumors leads to the discovery

of unusual genetic alterations in tumor that would be otherwise classified as papillary renal cell carcinoma (RCC). This is the case of the renal tumors associated with ALK translocations, a molecular trait that represent a target of therapy in lung cancer. These tumors display translocations of *ALK* with a large spectrum of partner genes including *TPM3*, *STRN*, *VCL*, *HOOK*, *CLIP1* and *KIF5B* (14).

Non-muscle invasive urothelial cancer may present as low-grade papillary or high-grade flat lesions. From the biological standpoint both lesions seem to share the loss of the *CDKN2* tumor suppressor gene encoding for the cell-cycle regulator p16 protein. While FGFR3 mutations drive the growth of low-grade lesions, p53 alterations are typical of flat carcinoma in situ (CIS) (15,16). The diagnosis of other superficial urothelial neoplasms such as the lesions with the typical inverted architecture have been supported by mutation of the MAP kinase/ERK pathway, while papillary urothelial neoplasms of low malignant potential (PUNLMP) are frequently related to promoter mutations of the telomerase *TERT* gene (17,18). *TERT* alterations do not occur in reactive urothelial lesion and this can be helpful in distinguishing low-grade neoplastic lesions from hyperplastic proliferations such florid cystic cystitis (19). The molecular classification of muscle-invasive bladder cancer represents one of the major recent innovations in the field of urothelial cancer. Several different laboratories in the last decade reached the same conclusions about the molecular subtypes of bladder cancer that has been recognized by The Cancer Genome Atlas (TCGA) consortium (20). Starting from a strange similarity with breast cancer, these gene expression-based classification recognizes the following molecular sub-types of urothelial cancer: (I) luminal tumors (as in the breast) mostly express genes of urothelial differentiation such as *GATA3* and uroplakin and frequently display mutations in *FGFR3* (16). (II) Basal-squamous tumors tend to express opposite genes typical of basal cells such as p63 or proteins as cytokeratins 5/6 and display variable mutations of *p53*. (III) A third, quite undefined, subtype had been named "p53-like", "luminal infiltrated" and it is characterized by retained *p53* function and moderate to intense inflammatory infiltrate (20). (IV) The neuronal-like subtype identifies small-cell neuro-endocrine bladder tumors. In the attempt to replicate the molecular classification using phenotypical markers pathologists have tried to use immunohistochemistry as surrogate of gene expression. Several phenotypic panels including GATA3, p63, CK5/6 and uroplakin have been proposed but none has reached the introduction in the clinical routine diagnostic practice so far (21,22).

Testicular cancer most likely derives from defective maturation of primordial germ cells and it is characterized by variable cytogenetic chromosome copy number gains/losses. The new WHO classification of testicular germ-cell tumors (TGCT) has re-grouped TGCTs into two categories according to the association with concomitant germ cell neoplasia in situ (GCNIS) and the age of onset. Type I and type 3 tumors such as pre-pubertal teratoma or spermatocytic seminoma do not originate from GCNIS while the vast majority of TGCTs such as seminoma, embryonal carcinoma, yolk-sac tumor and teratoma arising from GCNIS (3). The molecular hallmark of GCNIS is the gain of chromosome 12p, often leading to an isochromosome i(12p). From a diagnostic view-point the assessment of the i(12p) is helpful in distinguishing TGCT in the metastatic setting and particular in teratoma that developed a somatic malignancy, or to differentiate pre-pubertal versus post-pubertal type teratoma (23).

About half of penile cancers are associated with HPV infection (24). The WHO in 2016 has introduced a classification for penile cancer and pre-cancer based on the histological lesions associated or not with HPV infection (25). Since most of the HPV-related pre-cancer lesions progressing to invasive penile cancer are flat [HPV-related high-grade penile intraepithelial neoplasia (PeIN)] and are associated with high-risk HPV strains, the positive immunostaining for p16 is now widely used as a surrogate for HPV molecular testing by PCR or *in situ* hybridization (26,27). HPV- and p16-negative penile cancers represent a peculiar epidemiological subset of tumors (28). These tumors are supposed to develop in a background of chronic inflammation and progress through hyperplastic and well-differentiated histological lesions (differentiated PeIN). The molecular alterations at the basis of differentiated PeIN are currently unknown.

The role of molecular test for assisting the diagnosis of prostate cancer is limited to selected tumor settings. One is the identification of a prostatic primary origin in the setting of a multi-metastatic cancer dissemination at the disease's onset. Immunohistochemical markers of prostatic origin such as the tumor suppressor gene *NKX3.1* or prostate-specific antigen (PSA) are reliable in most cases (29). Notwithstanding, in certain anatomical sites (serosal cancer effusions or bone metastases) and in rare cases these markers can turn under-expressed or negative and histology may be overlapping. Molecular tests such as the identification of the TMPRSS2-ERG fusion, typical of at least 50%

Table 1 Novel biomarkers of possible future implementation in genitourinary cancer

Cancer type	Biomarkers type			
	Diagnostic	Prognostic	Predictive	Immunotherapy
Renal cell cancer	Mutation: *TSC2, TSC1*	*BAP1, SETD2, PBRM1*	*P53* (sarcomatoid neoplasia); *PBRM1*	Tumor inflammatory microenvironment
Urothelial cancer	Mutation: *FGFR3, TERT*	None	Amplification: *HER 2*; mutation: FGFR3	Inflammatory gene expression profiling; PD-L1 IIC; tumor mutational burden
Testicular cancer	Isochromosome 12p (FISH)	Mutation: *cKIT*	Alteration: *BRCA1, RAD51*	None
Penile cancer	None	None	None	PD-L1 IIC (tumor cell)
Prostate cancer	*TP53, RB1* in CRPC	Alteration: *PTEN*	DNA repair: *BRCA1, BRCA2, ATM*	Gene alteration: MMR

CRPC, castration resistant prostate cancer; MMR, mismatch repair.

prostate cancer or the amplification of the androgen receptor gene might be useful for diagnosis (30,31). The differential diagnosis between advanced prostate cancer with neuroendocrine (NE) differentiation versus primary small-cell NE cancer of the prostate represents another diagnostic dilemma for pathologists. Both these tumor types are likely associated with clinical resistance to therapeutic hormone castration and the immunohistochemical markers of NE or prostatic differentiation are often of little help (32). Unfortunately, both primary small-cell NE carcinoma of the prostate and prostate cancers with endocrine differentiation may express the same NE immunohistochemical markers and the morphology alone does not warrant the diagnosis in all cases. The identification of molecular markers such as the inactivation of TP53 or RB1, although not entirely specific, would help better separate castration resistant prostate cancer (CRPC) from small-cell NE neoplasms with important clinical implications (33). The increasing application of next-generation sequencing (NGS) technologies to advanced prostate cancer patients for therapeutic options (see below) will certainly improve also the diagnostics of the spectrum of NE prostatic lesions (34). Novel diagnostic molecular tests are summarized in *Table 1*.

Molecular prognostic and predictive biomarkers in genitourinary tumors

Oncologic therapy of metastatic RCC is currently based on tyrosine kinase inhibitors (TKIs) or inhibitors of the m-TOR pathway or immune check-point inhibitors (ICPI) (35). TKIs for RCC mainly deploy an anti-angiogenic consequence of the VHL inactivation in clear cell tumors through the simultaneous inhibition of several kinases including VEGFR, PDGFRA and MET. Personalized therapy of advanced RCC with TKIs is not guided by molecular tests to date. However, the use of NGS panels in RCC has recently disclosed alterations in novel genes such as *PBRM1*, *BAP1* and *SETD2*, all located close to the genetic locus of VHL on chromosome 3p. These genes are involved in chromatin remodeling and histone methylation. *BAP1* and *SETD2* mutations are associated with aggressive disease while *PBRM1* mutations seem to confer favorable prognosis (36). ALK-translocated RCC and pure sarcomatoid RCC represent two specific disease settings. The first unveils the potential application of anti-ALK TKIs as demonstrated in single case reports (37). The second is associated with a high frequency of TP53 alterations that leads to likely resistance to TKIs and favors the use of chemotherapy or immunotherapy in metastatic sarcomatoid cases (38). Immunotherapy with ICPI represents a major advance in the therapy of metastatic RCC with both clear-cell and non-clear-cell histology (39). The assessment of PD-L1 in RCC to predict response to ICPI is currently discouraged due to several limitations including the different antibodies and the different scoring systems (40). Additional predictors of response to ICPI including tumor mutational burden and assessment of the tumor inflammatory micro-environment are potentially promising but require prospective validations as biomarkers (41).

The molecular classification of invasive urothelial cancer has important therapeutic implications. In fact, advanced urothelial cancer of basal subtype is associated with higher response rates to cisplatin-based chemotherapy compared

to the other subtypes (42). Similarly, a distinctive trait of the "p53-like" subtype is the resistance to cisplatin-based regimens (43). The luminal subtype of urothelial cancer is characterized by mutations in *FGFR3*. Although the number of muscle-invasive cancers of the luminal type is lower compared to the other subtypes the presence of FGFR3 alterations could be target of specific anti-cancer agents such as the pan-FGFR inhibitor Erdafitinib and Infigratinib. In a phase II clinical trial Erdafitinib was associated with 40% objective tumor responses in 40% of patients with urothelial cancer harboring *FGFR* mutations (44). Although the micropapillary variant of urothelial cancer is typically enriched in HER2 amplification the attempt to apply the well-known HER2 targeting agents used in breast cancer to urothelial malignancies has provided quite disappointing results (45). Nevertheless, the over-expression of HER2 in bladder cancer is variable, is not only restricted to micropapillary tumors and the HER2 amplification is not always coupled with protein immunoreactivity (46). Therefore, new clinical trials testing anti-HER2 agents with different patients' selection criteria are required. Predictive biomarkers for immunotherapy with ICPI in urothelial cancer would require a separate review. Currently, the two PD-1/PD-L1 inhibitors Pembrolizumab and Atezolizumab are approved for first-line treatment of advanced urothelial cancer, and other ICPI such as Durvalumab, Avelumab and Nivolumab are approved for second-line (47). Approximately 20–30% of the patients display objective responses and some are long-lasting. Responses are more frequent among the basal and the p53-like immune-enriched molecular subtypes compared to the luminal type. As previously discussed for kidney cancer, the predictive test is based on the immunoreactivity for PD-L1 using different antibodies and different scoring systems and criteria according to each ICPI, weakening the role of immunohistochemistry as predictive biomarker (48). Molecular predictive factors of response to ICPI are more promising and are essentially based on the tumor mutation burden, inflammatory genes expression profiling and genomic instability (49). A recent trial has highlighted the synergy of combined proportional score for PD-L1 in immunohistochemistry plus tumor mutational burden in advanced urothelial cancer with predominant histological variants treated with neo-adjuvant Pembrolizumab (50). Clustering of inflammatory genes expression by gene set enrichment analyses recently turned out as a significant prognosticator in advanced urothelial cancer and was also used as a predictor of response in neo-adjuvant immunotherapy (51-53). It seems very likely that in the near future a combination of gene expression profiling for inflammatory genes, tumor mutational burden and the immunohistochemical expression of PD-L1 in inflammatory cells will be required before decision on neo-adjuvant immunotherapy in urothelial cancer.

The general good prognosis of post-pubertal testicular germ cell tumors (GCTs) and the excellent response to chemotherapy even in the advanced cases has limited the application of molecular analyses in testicular cancer. The Cancer Genome Atlas investigations on GCTs highlighted a large amount of cytogenetic alterations and a very low mutational load (54). The higher rate of mutations involves seminoma where the presence of *KIT* genetic variants seems associated with more intense inflammatory infiltrate and potentially regressions. On the contrary, *KIT* wild-type seminomas seem more prone to development towards other GC histotypes (54). Chemotherapy refractory GCTs represent a small subset of patients with few residual therapeutic options. The presence of alterations in BRCA1 or RAD51 in these patients discloses the potential option for a treatment with poly (ADP-ribose) polymerase (PARP) inhibitors (55).

Investigations on kinase pathways in penile cancer evidenced activation of the PTEN, STAT3, GNRH, IL-8 and B cell receptor signaling and gene overexpression of GNRH, NF-κB, STAT3, ERBB2 and 3 (56). However, no TKIs have been approved to date in penile cancer. Besides target therapy, the high rates of PD-L1 expression in squamous penile cancer, the strong correlation between PD-L1 immunoreactivity in primary tumors and metastases, and the high immunogenicity of the E6 and E7 HPV proteins make immunotherapy a feasible alternative therapeutic option with several ongoing trials (57,58).

PTEN and the consequent activation of the PI3K/AKT signaling pathway can be considered the most reliable biomarker of progression in prostate cancer (59). *PTEN* is usually lost in PCA due to deletions, truncations or inactivating mutations. Regardless of the mechanism the loss of PTEN function is invariably associated with PCA recurrence after surgery and PCA specific death (60,61). DNA repair deficiency represents the cutting edge of predictive biomarkers in PCA. Genes involved in the homologous recombination including *BRCA1/2* and *ATM* are enriched in lethal PCA and associated with a higher chance of developing resistance to castration in advanced cases (62,63). In this view, the PARP inhibitor Olaparib was able to improve the disease-free survival of CRPC patients

showing at least one alteration in *BRCA1/2* or *ATM* after failure of hormone therapy (64). Mismatch repair (MMR) is also impaired and enriched in advanced and histologically aggressive PCA compared to localized disease (65). Most PCA patients with MMR belong to Lynch families or develop sporadic mutations in the MMR genes. Although immunotherapy is not yet a therapeutic option for PCA it might represent a promising alternative in advancer patients with MMR alterations (66). Finally, the role of androgen receptor amplification and splicing variants has been deeply investigated in the last decade and associated to resistance to hormone blockade (67,68). Despite the emerging evidences linking AR alterations to resistance to castration the tests for the assessment of AR amplification and ARv7 expression did not enter yet in the clinical practice. New prognostic and predictive biomarkers are depicted in *Table 1*.

Wide genome analyses and mostly the TCGA initiative have shed light on the multi-faced genetic mechanisms behind the cancerogenesis and progression of genitourinary tumors. NGS technologies nowadays represent a simple and quite inexpensive tool to dissect the molecular alterations of single cancers. Genitourinary tumors represent the new frontier of the molecularly driven therapies and immunotherapies. The future is bright, we just need to look at it with critical eyes.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Rodolfo Montironi, Alessia Cimadamore, Antonio Lopez-Beltran, Marina Scarpelli and Liang Cheng) for the series "Update on Molecular Classification and Individualized Treatments of Genitourinary Tumors" published in *Translational Andrology and Urology*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/tau-20-1185

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-20-1185). The series "Update on Molecular Classification and Individualized Treatments of Genitourinary Tumors" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Giunchi F, Franceschini T, Fiorentino M. A narrative review of individualized treatments of genitourinary tumors: is the future brighter with molecular evaluations? Transl Androl Urol 2021;10(3):1553-1561. doi: 10.21037/tau-20-1185

