Review Article
Background, applications and challenges of radiogenomics in genitourinary tumor

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Abstract: Genitourinary tumors are groups of tumors with high complexity and heterogeneity. For long-term monitoring, biomarkers that can be used in detection, grading and treatment response assessment are needed. With rapid development in imaging technology and cancer genomics, radiogenomics, the combination of "radiology" and "genomics", has emerged as a powerful tool in oncology practice in recent years because imaging can provide some information that genomic test cannot as gene expression and mutation status are usually evaluated on a small portion of the tumor and are usually not powerful enough to reflect tumor heterogeneity. Radiogenomics investigates the correlations between imaging features and gene expression of a disease, especially in oncologic diseases. It aims to detect the disease's mutation status and supplement genomic analysis based on imaging analysis, providing additional findings for diagnosis, treatment decisions, evaluation of treatment response and prognosis prediction of the disease. Recent years have seen an increase in the number of studies investigating the application of radiogenomics in genitourinary tumors. Many studies have shown promising results. However, there still exist limitations and challenges. In this review, we will summarize recent applications of radiogenomics in genitourinary tumors and discuss limitiations, challenges and future directions of radiogenomics.

Keywords: Genitourinary tumors, radiogenomics, gene mutation, mutation status

Introduction

Genitourinary tumor is a group of tumor with high complexity and heterogeneity. Considering these tumors' biologically diversity, a careful long-term monitoring is required. Thus, non-invasive biomarkers that have the potential to be applied in tumor description and diagnosis, stratification of risk, management decision, treatment monitoring and outcome prediction are of urgent need.

Traditionally, imaging tests have been used to get a primary diagnosis and clinical stage of the disease in genitourinary tumors. Recent progress in imaging modalities and Omics has contributed to the establishment of new methods for a better tumor characterization and for detecting biomarkers that are useful in early diagnosis and prognosis [1, 2]. Radiomics, also known as computational imaging analysis, re-fers to the process of transforming conventional medical images into high-dimensional, mineable data [3-5]. It has emerged as a powerful tool in oncologic practice in recent years [3-5].

With the rapid development in radiomics and cancer genomics, radiogenomics has also gained popularity recently. It is important to understand that radiogenomics and radiomics are different. Radiogenomics investigates the associations between imaging features and gene expression of a disease, especially in oncologic diseases [6, 7]. It aims to non-invasively detect mutation status of a disease and supplement genomic analysis based on imaging analysis, providing additional results for diagnosis processes, evaluation of treatment response and prognosis prediction [8, 9]. Data that cannot be extracted from genomic test in turn may be mined by radiogenomics from images as gene expression and mutation status are evaluated

on a small portion of the tumor and are not powerful enough to reflect tumor heterogeneity [9, 10]. Through a deep characterization of tumor heterogeneity, we can get a better understanding of tumor development and progression. Finally, by applying radiogenomics, we can develop imaging biomarkers that have the potential to stratify risk and predict survival, thus enabling a better precision medicine [11]. In this review, we will summarize recent applications and development of radiogenomics in genitourinary tumors and discuss limitations, challenges and future directions.

Radiogenomics in renal cell carcinoma

Recent years have seen a significant advance in the identification of multiple mutations associated with renal cell carcinoma (RCC) [12-17]. Von Hippel-Lindau (VHL) tumor suppressor gene is identified as the most common mutation in clear cell renal cell carcinoma (ccRCC) [18]. However, no predictive or prognostic value of VHL gene mutation was detected in ccRCC patients [19]. Recently, genomics analysis of ccRCC has yielded alterations such as polybromo-1 (PBRM1), BRCA1-associated protein 1 (BAP1), SET domain containing 2 (SETD2) and lysine-specific demethylase 5C (KDM5C) [14, 20-23]. Considering that biopsy-generated genetic data from tumor may be undermined by high intratumoral heterogeneity observed in RCC, radiogenomics has significant value as imaging can reflect genomic information of the tumor not covered by biopsy.

It has been reported that associations between imaging features and mutation status could be detected in ccRCC. Shinagare et al. discovered that BAP1 mutation was associated with ill-defined margins and calcification while mucin 4 (MUC4) mutation correlated with exophytic growth pattern of the tumor [24]. Mutation of BAP1 is detected in about 15% of ccRCC and is associated with high Fuhrman grade and poor overall survival (OS) [25]. This result helps to explain that ill-defined tumor margins in some ccRCC could predict a high tumor grade and poor OS. Studies have revealed that mutation of MUC4 correlated with an improved survival in ccRCC [26]. Combing the findings from Shinagare et al., it may explain why exophytic growth pattern could indicate an improved survival in patients with ccRCC. Associations

between CT imaging features and mutation status of VHL, PBRM1, SETD2, BAP1 and KDM5C in ccRCC were also investigated [27]. KDM5C and BAP1 mutations were significantly associated with renal vein invasion. Mutations of VHL were significantly associated with well-defined tumor margins, nodular tumor enhancement and intratumoral vascularity gross appearance on contrast-enhanced CT scan. While mutations of VHL and PBRM1 were more commonly identified in solid ccRCC, SETD2, KDM5C and BAP1 mutations were undetectable in multicystic ccRCC. Considering the prognostic information of these gene mutations, these studies support the use of radiogenomics in aiding in management and decision-making of ccRCC. A simple overview of the mutated genes and their associated imaging features in ccRCC was shown in **Figure 1**.

Ghosh et al. constructed CT-based model for predicting the BAP1 gene mutation status. The model achieved area under the receiver operating characteristic curve (AUC) values of 0.71, 0.66, 0.62, 0.52 for the nephrographic, unenhanced, cortico-medullary and excretory CT images, respectively [16]. For predicting mutation status of VHL, PBRM1 and BAP1, Chen et al. utilized different classifiers, constructing a multi-classifier radiogenomics model based on quantitative CT features [27]. The model achieved an AUC value of more than 0.85 for predicting these three genes. Compared with individual classifiers, the multi-classifier achieved a better performance. Recently, Kocak et al. investigated the value of texture analysis based on unenhanced CT scan in predicting BAP1 mutation status in ccRCC [21]. The texture analysis achieved a high specificity, sensitivity and precision in predicting BAP1 mutation status in ccRCC.

The tumor suppressor gene PBRM1 is the second most frequently identified gene mutation in ccRCC. A mutated PBRM1 gene correlated with poor prognosis and advanced clinicopathological features in ccRCC patients [28]. Recent studies revealed that mutational status of PBRM1 may affect the treatment response to VEGF-targeted therapy and immune checkpoint inhibitors in advanced or metastatic ccRCC [29, 30]. Kocak et al. utlilized high-dimensional quantitative CT texture features to develop classifiers for prediction of PBRM1 mutation
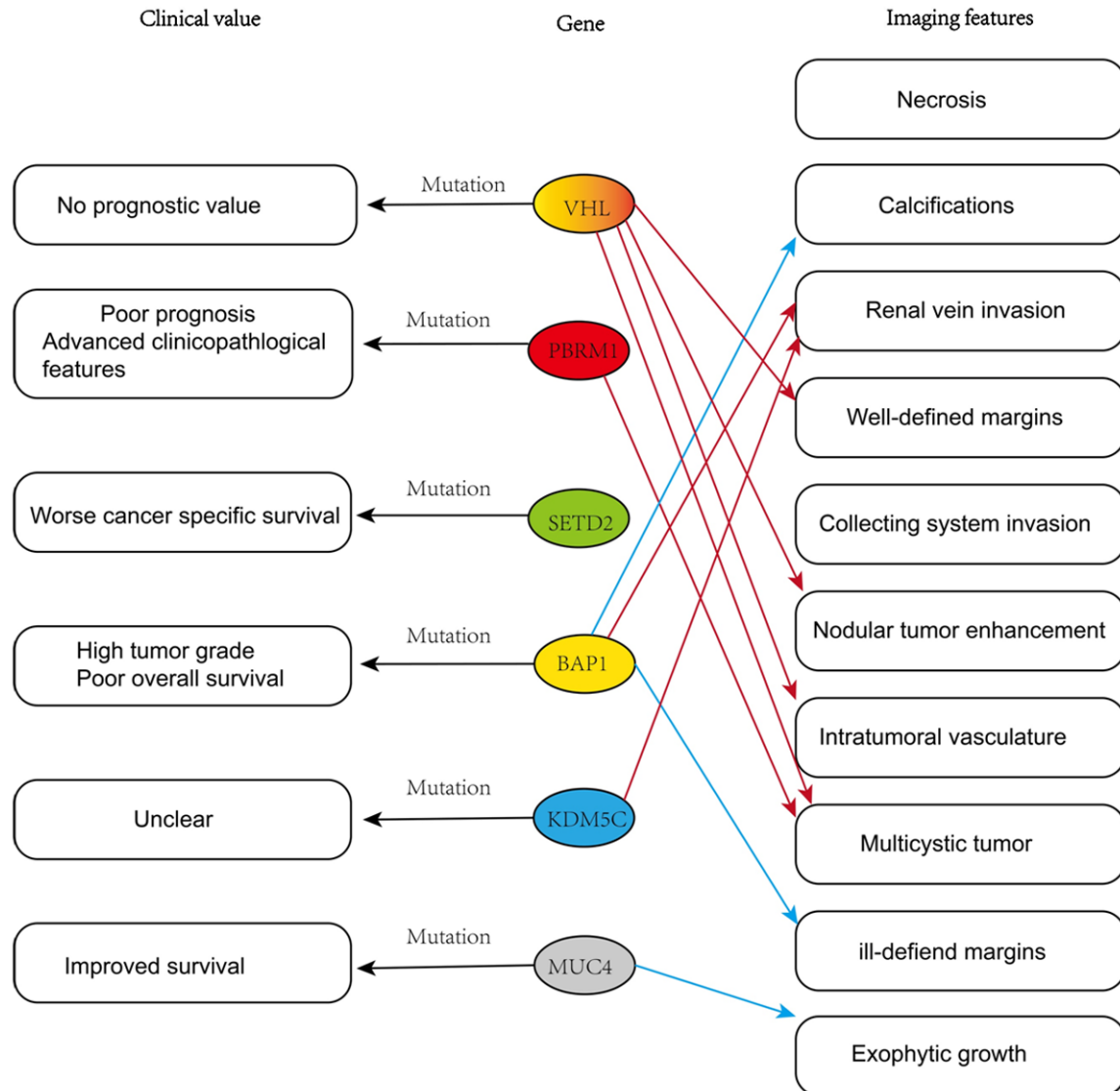
Figure 1. Overview of the mutated genes and their associated imaging features in ccRCC. Red arrow: associations identified by Karlo et al.; Blue arrow: associations identified by Shinagare et al.

[17]. The machine-learning artificial neural network (ANN) algorithm achieved an accuracy of 88.2% with an AUC of 0.925. The machine-learning random forest (RF) algorithm outperformed the ANN algorithm with an accuracy of 95.0% and an AUC of 0.987.

Recently, microRNA (miRNA) is recognized to play an important role in ccRCC tumorigenesis [12, 31]. It also significantly correlated with patient outcome [32, 33]. In a study by Marigliano et al., a promising association between miRNA and CT texture analysis has been identified in ccRCC [13]. Particularly, miR-21-5p, a pivotal miRNA involved in ccRCC tumorigenesis

and entropy, a texture analysis parameter, showed good correlation in ccRCC. Texture analysis may have the potential to serve as a non-invasive method for ccRCC evaluation.

Due to an increase in imaging modalities performed in the last few years, lots of RCCs were first identified at pathological T1 (pT1) with a 5-year survival rate of 97%, which means that most localized RCC can be surgically removed [34]. However, RCCs could show different aggressiveness and diverse outcomes [35, 36]. It is reported that about 30% of patients with localized RCC at the time of surgery finally recur and metastasize. These patients have an

unfavorable prognosis with a 5-year survival rate of 12% [34, 35]. Thus, the development of biomarkers to predict metastasis is of urgent need to select patients that are most likely to benefit from adjuvant therapy. Lee et al. found that four radiomics features extracted from the nephrographic phase of postcontrast CT could predict postoperative metastasis of pT1 RCC patients and these four radiomics features were correlated with heterogenous-trait-associated gene signatures [36]. The result of the study showed that radiogenomics could aid in enacting more effective adjuvant therapies for patients with pT1 RCC demonstrating postoperative metastasis.

It is now widely acknowledged that combined analysis of several biomarkers is the most promising method that may have the potential to change clinical management [37, 38]. Utilizing clinical data, genetic profiles and preoperative contrast-enhanced CT images, Jamshidi et al. constructed a radiogenomic risk score (RRS) for ccRCC [38]. The result showed that both in the training and validation group, a lower disease-specific survival was detected in high RRS group regardless of stage, grade and performance status. Given the promising results of RRS in ccRCC, Jamshidi et al. evaluated the value of RSS in stratifying radiological progression-free survival (rPFS) of patients with metastatic RCC treating with bevacizumab before surgery [39]. Based on pretreatment CT, the rPFS to bevacizumab could be successfully stratified by RRS with a median PFS of >25 versus 6 months and OS of >37 versus 25 months in the low and high RRS groups, respectively.

Radiogenomics in bladder cancer

As a highly complex and heterogeneous tumor, a careful long-term monitoring plays a vital role in the management of bladder cancer (BCa). However, effective, non-invasive biomarkers for BCa management are still lacking. The clinical staging system fails to predict the prognosis of BCa accurately or aid in treatment decision [40]. Lin et al. developed an integrative nomogram incorporating contrast-enhanced CT radiomics, RNA sequencing data and clinical data [41]. The nomogram showed an excellent ability for predicting progression-free interval in BCa patients. The radiomics signature developed in the study could reflect the angiogenesis status of BCa.

Radiogenomics in prostate cancer

Genes like phosphatase and tensin homolog (PTEN) and vmyc avian myelocytomatosis viral oncogene homolog (MYC) have shown prognostic value for outcome parameters like biochemical recurrence, metastasis and mortality in prostate cancer (PCa) [42]. Mutations or deletions in tumor suppressor gene PTEN have been discovered in certain tumors [43]. Multiparametric MRI (mp-MRI) is playing an vital role in PCa management. The associations between cancer aggressiveness and mp-MRI features have been investigated [44]. However, associations between MRI features and genomic markers are still lacking. McCann et al. investigated the associations between quantitative mp-MRI imaging features of the prostate and PTEN expression of peripheral zone PCa [45]. The result revealed that there existed a weak negative correlation between the quantitative feature Kep and PTEN expression. Hypoxia has been proved to correlate with local and distal failure in certain solid tumors treated with radiotherapy [46]. It is known that hypoxia exists in PCa. However, evaluation of hypoxia remains difficult as studies concerning in vivo hypoxia imaging in PCa is limited [47, 48]. Sun et al. tried to investigate correlation between imaging features of mp-MRI and hypoxia-related gene expression in PCa [49]. 34 imaging features including 28 from T2 weighted (T2W) imaging-texture features and 6 from the mp-MRI data were identified by correlation analysis. Finally, 16 out of the 28 T2W texture features were associated with hypoxia gene expressions. This finding could aid in hypoxia-related treatment selection.

Stoyanova et al. studied the association between imaging features of quantitative mp-MRI and gene expression in PCa using mp-MRI-directed prostate biopsies [50]. Gene expression data was generated using an Affimetrix platform. Radiomics parameters were extracted from areas of biopsy regions and normal appearing tissues. There were significant correlations between quantitative imaging features and genes. There were also strong associations between radiomics features and significantly expressed genes. In recent years, mp-MRI and prostate specific membrane antigen (PSMA)-positron emission tomography/computed tomography (PSMA PET-CT) has gained popularity in radiological evaluation of

PCa. However, whether imaging-detected lesions correlate with gene data of PCa remains unknown. Kesch et al. tried to define a genomic index lesion using chromosomal copy number alterations (CNAs) as markers for tumor aggressiveness in relation to imaging features of mp-MRI and PSMA PET-CT [51]. The result revealed that there existed a strong correlation between imaging features and genomic index lesions. Radiogenomics may have potential to aid in differentiating between indolent and aggressive PCa.

Jamshidi et al. evaluated the prostate microenvironment using mp-MRI and DNA whole-exome sequencing in patients with prostate adenocarcinoma [52]. The results showed that whole-exome radiogenomics analysis and mp-MRI imaging shows a continuum of mutations across regions that were found to be high grade and normal grade by histological assessment in patients with prostate adenocarcinoma. Wibmer et al. explored the associations between MRI imaging features and cell cycle genes expression levels [53]. It turned out that patients with extracapsular extension (ECE) on MRI imaging had a higher mean cell cycle risk scores, indicating that ECE may represent a more aggressive genomic profile of PCa.

A precise prediction of pathological PCa stage would help clinicians better determine treatment choices. Fischer et al. developed a radiogenomics approach based on clinical, imaging and two genomic features [2]. The model has high potential to reveal the molecular mechanisms underlying tumor aggressiveness and predict tumor pathological stage. Published studies on radiogenomics in genitourinary tumor is summarized in **Table 1**.

Challenges and future directions

Thus far, a number of radiogenomics studies have been carried out in genitourinary tumors, especially in RCC and PCa. Studies focusing on other tumors including BCa, testicular cancer, penis cancer and renal pelvic cancer are still lacking. Radiogenomics investigates the associations of imaging data with genomic data, enabling a deeper understanding of underlying tumor biology. It may have the potential to be applied in other genitourinary tumors.

There are several significant issues concerning radiogenomics that require our attention [54].

Radiogenomics aims to correlate imaging data with genomic data that have clinical significance. However, some radiogenomics studies established relationships between genomic data and imaging features, some of which are not related to prognostic outcomes. Considering that mechanism of gene expression and signaling pathways are complex, linking imaging features to genomic data directly may cause bias. Additionally, radiogenomics studies are prone to statistically over-fitting issues as matching imaging data with huge amount of genomic data remains difficult. Commonly, individual genetic mutations would be grouped into gene traits before associating them with imaging data. However, it could undermine the ability of imaging in predicting outcomes. Additionally, inter-observer variation exists in qualitative imaging features, which means that sometimes evaluation of qualitative imaging features is needed.

Although some radiogenomics studies have shown promising results, it should be acknowledged that current studies are mainly performed on small sample sizes. It may be difficult to select patients with both enough tumor samples for genomic analysis and images for image analysis [54]. Compared to imaging data, genetic data still remains limited and performing genetic tests prospectively is expensive. Public data resources like The Cancer Imaging Archive (TCIA) and The Cancer Genome Atlas (TCGA) may be potential solutions. The retrospective nature of the studies would also result in limitations. In the future, a well-designed multicenter prospective study with large data set should be carried out. Another important limitation is the issue of standardization. Imaging acquisition, segmentation methods, and reconstruction protocols may differ significantly among centers and scanners. The results of radiogenomics could be influenced.

Genomic data in radiogenomic studies are mostly obtained from microarray data. Studies focusing on the role of microRNAs are lacking. As these RNAs have the potential to target large number of genes and regulate gene expression, studies correlating these RNAs with imaging data may be a new direction.

In the future, with advances in artificial intelligence (AI) techniques, high-throughput technologies and imaging technologies, we may enter the new era of "omics" research. With

Table 1. Published radiogenomics studies in genitourinary tumor

References	Tumor	Application	Results
Shinagare et al. [24]	ccRCC	Association between imaging features and gene mutation	BAP1 mutation was associated with ill-defined margins and calcification. MUC4 mutation correlated with exophytic growth pattern of the tumor
Karlo et al. [26]	ccRCC	Association between imaging features and gene mutation	KDM5C and BAP1 mutations were associated with renal vein invasion. Mutations of VHL were associated with well-defined tumor margins, nodular tumor enhancement and intratumoral vascularity gross appearance
Ghosh et al. [16]	ccRCC	Predicting BAP1 mutation status	CT-based model achieved AUC values of 0.71, 0.66, 0.62, 0.52 for the nephrographic, unenhanced, cortico-medullary and excretory CT images, respectively
Chen et al. [27]	ccRCC	Predicting mutation status of VHL, PBRM1 and BAP1.	The multi-classifier model achieved a AUC value of more than 0.85 in predicting these gene mutations
Kocal et al. [21]	ccRCC	Predicting BAP1 mutation status	Texture analysis based on unenhanced CT achieved a high specificity, sensitivity and precision in predicting BAP1 mutation status
Kocal et al. [17]	ccRCC	Predicting PBRM1 mutation status	The RF algorithm outperformed the ANN algorithm with an accuracy of 95.0% and an AUC of 0.987
Marigliano et al. [13]	ccRCC	Association between miRNAs and texture features	miR-21-5p and entropy showed good correlation in ccRCC
Lee et al. [36]	RCC	Predicting postoperative metastasis of RCC	Four radiomics features extracted from the nephrographic phase of postcontrast CT could predict postoperative metastasis of pT1 RCC patients and these features were correlated with heterogenous-trait-associated gene signatures
Jamshidi et al. [38]	ccRCC	Predicting prognosis	Radiogenomic risk score (RRS) could stratify radiological rPFS of patients with metastatic RCC treating with bevacizumab before surgery
Lin et al. [41]	BCa	Predicting prognosis	The nomogram incorporating contrast-enhanced CT radiomics, RNA sequencing data and clinical data showed an excellent ability for predicting progression-free interval in BCa patients
McCann et al. [45]	PCa	Association between imaging features and gene expression	There existed a weak negative correlation between the quantitative mp-MRI imaging feature Kep and PTEN expression in PCa
Sun et al. [49]	PCa	Association between imaging features and gene expression	16 T2W texture features were associated with hypoxia gene expressions in PCa
Stoyanova et al. [50]	PCa	Association between imaging features and gene expression	There were significant correlations between quantitative imaging features and genes in PCa
Kesch et al. [51]	PCa	Predicting tumor aggressiveness	A strong correlation between imaging features and genomic index lesions was detected
Jamshidi et al. [52]	PCa	Prostate microenvironment evaluation	Whole-exome radiogenomics analysis and mp-MRI imaging shows a continuum of mutations across regions that were found to be high grade and normal grade by histological assessment.
Wibmer et al. [53]	PCa	Association between imaging features and gene expression	Patients with extracapsular extension (ECE) on MRI imaging had a higher mean cell cycle risk scores
Fischer et al. [2]	PCa	Prediction of pathological stage	The radiogenomics model has high potential to reveal the molecular mechanisms underlying tumor aggressiveness and predict tumor pathological stage

imaging data combing with genomic, transcriptomic, proteomic and metabolomic data, multi-dimensional studies could be carried out in genitourinary tumors, aiming at the ultimate goal of precision medicine.

Disclosure of conflict of interest

None.

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