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Review Article

Applications of radiomics in genitourinary tumors

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Abstract: Genitourinary tumors are heterogeneous groups of tumors with high morbidity and mortality rates. Confronted with existing problems in the management of genitourinary tumors, a personalized imaging method called radiomics shows great potential in areas including detection, grading, and treatment response assessment. Radiomics is characterized by extraction of quantitative imaging features which are not visible to the naked eye from conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT), followed by data analysis and model building. It outperforms other invasive methods in terms of non-invasiveness, low cost and high efficiency. Recently, a number of studies have evaluated the application of radiomics in patients with genitourinary tumors with promising data. The combination of radiomics and clinical/laboratory factors provides added value in many studies. Despite this, there are limitations and challenges to be overcome before a more extensive clinical application in the future. In this article, we will introduce the concept, significance and workflow of radiomics, review their current applications in patients with genitourinary tumors and discuss limitations and future directions of radiomics. It would help multidisciplinary team involved in the treatment of patients with genitourinary tumors to achieve a better understanding of the results of radiomics study toward a personalized medicine.

Keywords: Radiomics, genitourinary tumors, radiogenomics, tumor grading, tumor differentiation, treatment response

Introduction

Genitourinary tumors remain both clinically and biologically heterogeneous with a high incidence rate and mortality [1]. Thus, biomarkers that can be applied to predict tumor subtypes, disease progression and treatment responses are gaining popularity. A personalized disease management is of urgent need. Considering the important role of imaging analysis in the screen, detection and overall management of genitourinary tumors, a new quantitative, reader-independent imaging-based strategy may have the potential to improve clinical care as traditional imaging analysis mainly bases on the anatomic changes and relies heavily on subject interpretation by radiologists, which are prone to variability. Radiomics refers to the method which converts digital medical images into high-dimensional, mineable data via extraction of quantitative descriptors, followed by data analysis and model building for aiding clinical decisions [2]. By quantitatively analyzing digital imaging, radiomics can potentially detect specific characteristics of a disease that otherwise could not be accessed visually with a potential to inform future precision medicine. Recent results have shown promising results of radiomics in oncological practice [2]. This method may supplement traditional imaging analysis and assist in providing personalized medicine for patients [3, 4].

Recent years have seen a rapid increase in the publications of the application of radiomics in the genitourinary tumors. In this review, we will

introduce the concept, significance and the workflow of the radiomics, review recent applications of the radiomics in the genitourinary tumors and discuss limitations and future directions of radiomics.

Concept and significance of radiomics

Precision medicine, in which the right treatment was based on the characteristics of different subtypes, has substantially changed treatment options in recent years. Robust and reliable biomarkers are essential to facilitating precision medicine development. Efforts are under way to develop such biomarkers all over the world. Unfortunately, current tumor evaluation is far from satisfaction. Subjective, qualitative features are usually used by radiologists to evaluate tumor characteristics, making the results less reliable.

Current assessment for gene expression and immune phenotype is mainly based on the biopsy and surgery, which may be less accurate due to intratumoral heterogeneity, let alone the procedure is expensive and invasive. Thus, the need for a non-invasive, stable and less expensive method has never been greater.

Radiomics was first introduced in 2012 by Lambin et al. [5]. It was motivated by the underlying hypothesis that medical imaging contains much more information than we have already acquired and the information can reflect underlying pathphysiology [6, 7]. By applying quantitative image analysis, the relationship between the information and the pathphysiology can be revealed. With subsequent model building, radiomics has the potential to aid clinical decisions and change clinical management. In oncological practice, radiomics has advantages over other methods. Imaging examinations are usually prescribed for almost every patient with cancer, which means that all these images are huge potential sources of radiomics data. It is safe, reproducible and easy to obtain. It is now widely accepted that most solid malignant tumors are highly heterogeneous at the phenotypic, physiologic and genomic levels [8-10]. Radiomics has shown great potential as a source of quantitative biomarkers to relate imaging features to intratumoral heterogeneity and biology phenotypes. In addition to tumor assessment, radiomics can achieve longitudinal evaluation of treatment response and disease progression. It is a promising method in the era of precision medicine.

Radiomics workflow

The practice of radiomics involve four main steps: (1) Imaging acquisition; (2) Volume of interest segmentation; (3) Feature extraction; (4) Models establishment.

Imaging acquisition

As the first step in radiomics, imaging acquisition would lay a solid foundation for subsequent steps of radiomics. Generally speaking, imaging data can be obtained from various imaging modalities like CT, MRI, PET-CT and ultrasound. Modern imaging units allow for difference in imaging protocols across medical centers. It is not a problem in the routine identification of imaging features used in clinical setting. However, when it comes to data extraction from images, variations in imaging protocols can introduce changes that are not resulting from underlying biologic effects [6]. Previous studies have revealed that radiologic features differ in different imaging acquisition parameters [11, 12]. Both spatial resolution and gray level resolution can affect the computation of radiomics features [13].

The accuracy and reproducibility of the radiomics results rely on the quality of image acquisition. It would be ideal for radiomics analysis to use standardized imaging protocols. Thus, imaging data should be preprocessed before feature extraction in order to ensure consistency and comparability. Heterogeneous spatial resolution can be resolved by resampling the voxels into isotropic pixels or voxels after co-registration of multi-spectral imaging modality or different sequences in the same imaging modality, and intensity normalization can be applied to solve the heterogeneous gray level resolution [14].

Volume of interest segmentation

Accurate identification and segmentation, defined as the Volume of Interest (VOI), is a key and challenging step in the radiomics analysis, as it defines the volume of the image from which the subsequent radiomics features are extracted. VOI can be segmented either manually, semi-automatically or automatically [7, 15].

Manual segmentation is a straightforward solution and is regarded as the "golden standard". However, apart from being burdensome and time-consuming, this process is affected by intra-operator and inter-operator variability [16-18]. Recent years have seen progression in the development of semi-automatically and automatically segmentation methods. Even we have so many available methods at hand, we must realize that there is no universal segmentation method fitting for all types of images. A segmentation method with high accuracy, high efficiency, maximal automation and reproducibility is of great need.

Feature extraction

Following VOI segmentation, various quantitative features can be extract from the identified VOI. The radiomics features can usually be classified into four categories: (1) Size and shape characteristics; (2) First-order statistical characteristics; (3) Second-order statistical characteristics; (4) Transform-based features. Size and shape characteristics describe the size and shape of the VOI, such as the volume of VOI, maximal surface area, tumor compactness and eccentricity and surface to volume ratio. First-order statistical characteristics describe the features related to the distribution of the intensities of voxels within the VOI, but do not describe its spatial arrangement, including the mean, median, maximum and minimum of voxel intensity, standard deviation, skewness, kurtosis, uniformity, and randomness. Second-order statistical characteristics, also known as texture features, was introduced by Haralick et al. [19]. The image texture means the perceived or measured spatial variation in the intensity levels. It can be visualized using a gray level scale. Texture features and higher features can be calculated from different matrices: the gray-level co-occurrence matrix (GLCM), the Gray Level Size Zone Matrix (GLSZM), the gray level run-length matrix (GLRLM) and the neighborhood gray-tone difference matrix (NGTDM) [20]. Texture features provide heterogeneity information among the lesions. Transform-based features aim to identify repetitive or non-repetitive patterns through imposing kernel functional transformation to the segmented image content [20].

Models establishment

It usually involves three aspects to build a radiomics model: feature selection, modeling methodology and model validation. One important specificity in radiomics analysis is the huge number of features imaging software can provide. It has recently been highlighted that too many features may lead to a high false-positive risk [15, 21, 22]. Thus, it is of vital importance to select features for further study to avoid overfitting. Two common procedures exist in determining radiomics features. One is to analyze generated features preliminarily and select features with most repeatability and reproducibility [23]. Another is to make a priori selection of features based on the features' mathematical definitions and select targeted features [24].

When the ideal features have been selected, they can be used for model construction. The methods selected for data analysis is dependent on several factors, including sample size and the application of radiomics measurements. There is a wide selection of statistical methods and machine learning (ML) algorithms for radiomics analysis, including nomograms, linear regression, logistic regression, random forest (RAF) and Cox proportional hazards regression [25]. The model selected would affect the performance of the radiomics analysis for assessing the prediction target [26]. For small pilot studies where a large sample size is impossible, univariate analysis may be a preferred selection [27]. While small pilot or retrospective studies can provide preliminary information that certain radiomics features or statistical methods are worth further mining as imaging biomarkers and surrogates for tumor biology, it is noteworthy that selection bias and false-positive results exist when the number of radiomics features assessed exceeds the number of enrolled patients [15]. Thus, it is highly recommendable that several models should be tested to select the model with best performance [28].

As the last and indispensable step in model building, model validation aims at assessing the performance and applicability of the radiomics model developed. Internal and/or external validation should be performed to ensure the generalizability of the model to all of the targeted patients. The receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) can be used to calculate the performance of the model. ROC curve can display the ability of disease recognition at any

threshold in an easy way. When comparing two or more models, the ROC curves can show advantages and disadvantages of the models in a visual way through drawing each model in the same coordinate [7].

Radiomics application in bladder cancer

Tumor staging and grading have important clinical significance for the management of bladder cancer (BCa). Based on CT urography, Garapati et al. constructed a predictive model as a classifier for stratifying BCa into two categories: below stage T2 and greater than or equal to stage T2 [29]. Machine learning methods including linear discriminant analysis (LDA), neural network (NN), support vector machine (SVM) and RAF classifiers were used in the study and these four classifiers showed comparable results in bladder cancer staging accuracy, demonstrating the potential application of radiomics in assessing BCa stage [29]. MRI also plays an important role in the clinical care of BCa. A recent study revealed that MRI texture features extracted from diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps were able to distinguish low- and high-grade BCa with an accuracy of 83% [30]. Multiparametric MRI (mp-MRI) has gained popularity in recent years. A mp-MRI based radiomics model was developed by Wang et al. and had the potential to serve as a noninvasive imaging approach for preoperative grading of BCa tumors [31]. The joint model constructed from T2WI, DWI and ADC features demonstrated a higher diagnostic accuracy than other single-modality models for preoperative prediction of pathological grade in BCa tumors [31]. All these studies showed promising feasibility of radiomics and laid a solid foundation for future application in bladder cancer staging and grading.

Due to poorer survival rate of micropapillary carcinoma (MPC) of the bladder compared with urothelial carcinoma (UC) of the bladder, earlier detection of MPC subtype would improve patient outcomes regardless of the treatment strategy [32, 33]. However, MPC subtype is difficult to distinguish from UC subtype during cystoscopy and on CT scans. A CT-based radiomics analysis revealed that compared to UC, MPC subtype has a more heterogeneous texture. Tumor heterogeneity extracted using GLCM and gray level difference matrix (GLDM) may be a noninvasive imaging strategy in separating MPC subtype from UC subtype. Evaluation of the depth of bladder cancer invasion is of great significance in the determination of treatment methods. Due to the unsatisfactory diagnostic accuracy of cystoscopy and histological evaluation of biopsy or resected tissue in diagnosing and staging BCa, CT and MRI are also performed to aid in preoperative tumor staging [34-39]. MRI could provide favorable soft-tissue contrast, leading to a better discrimination between non-muscle-invasive BCa (NMIBC) and muscle-invasive BCa (MIBC) than CT [40]. T2-weighted imaging in MRI is able to directly evaluate the depth of BCa involvement [41]. However, its application is still limited due to unsatisfactory diagnostic accuracy with a range between 64.7% and 83% [42-45]. Zheng et al. developed a MRI-based radiomics-clinical nomogram, showing a favorable result in discriminating NMIBC from MIBC with an AUC of 0.922 in the training set and an AUC of 0.876 in the validation set [46]. Another study aiming at accurately differentiating between NMIBC and MIBC based on MRI radiomics features achieved a result with the AUC and Youden index improving to 0.8610 and 0.7192, respectively [47]. A T2-weighted MRI-based radiomics also showed a promising result in classifying BCa into different stage groups (non-muscle invasive vs muscle-invasive), which may improve BCa clinical staging and aid in therapy management [48].

Lymph node (LN) metastasis is a negative prognosis indicator in patients with BCa. Compared to LN-negative patients, LN-positive patients have a lower 5-year overall survival rate (15-31% VS >60%) [49, 50]. Accurate preoperative prediction of LN status in patients with BCa can aid in clinical decision-making. CT and MRI are usually used in nodal staging in patients with BCa. However, both imaging modalities evaluate LN status according to their sizes, while a considerable part of malignant LNs remain a normal or minimally-enlarged size in BCa. Therefore, the sensitivity of CT or MRI for detecting LN metastasis is relatively low (31-45%), resulting in a proportion of patients being understaged [51-53]. Wu et al. developed two nomograms based on CT radiomics features and MRI radiomics features, respectively [54, 55]. The CT-based radiomics nomogram that incorporates the radiomics signature and

CT-reported LN status has the potential be used as a non-invasive imaging approach for individualized preoperative prediction of LN metastasis in BCa [54]. The MRI-based radiomics nomogram consisting of the radiomics signature and MRI-reported LN status shows favorable predictive accuracy for LN metastasis in BCa, with an AUC of 0.9118 in the training set and an AUC of 0.8902 in the validation set [55].

Realizing the importance of preoperative prediction of the recurrence risk of BCa, Xu et al. developed a nomogram based on MRI radiomics and clinical predictors for individualized prediction of the first 2 years (TFTY) risk in recurrence [56]. The nomogram combined the Rad Score and important clinical factors including age, gender, tumor grade, muscle-invasive status (MIS) of the lesion, tumor size, number and previous history of surgery, showing excellent performance in both the validation and training set. When the risk threshold was larger than 0.3, the decision curve showed that the radiomics-clinical nomogram can provide more benefit than using the radiomics or clinical model alone.

Neoadjuvant chemotherapy (NAC) plays an important role in the management of BCa. However, no reliable methods are available to predict a patient's response to NAC. Patients may experience side effects of chemotherapy while enduring the risk of no benefit from the chemotherapy. Thus, early evaluation of treatment response and prediction of treatment failure are important, allowing clinicians to withdrawal unbeneficial treatment timely. Cha et al. developed radiomics models based on CT images obtained before or after neoadjuvant chemotherapy in discriminating BCa with chemotherapy responses or not. The study revealed that radiomics has the potential to aid in the evaluation of therapy responses [57]. The application of radiomics in BCa is summarized in **Table 1**.

Radiomics application in kidney cancer

Recent years have seen a significant increase in the incidence of renal masses due to large amounts of imaging studies carried out. Most renal masses are usually considered as malignant and require surgical resection [58]. However, it has been revealed that 13%-16% of surgically resected renal masses are benign [59]. Thus, it is important to differentiate benign renal masses from malignant renal masses to avoid unnecessary surgeries. However, no existing imaging modalities are capable to make a 100% differential diagnosis due to the similarities in the imaging findings between benign and malignant renal masses. Considering the invasive character and potential risk of renal biopsy, a non-invasive method is of urgent need.

Yan et al. showed that CT texture analysis may be a reliable quantitative imaging approach to differentiate between clear cell RCC (ccRCC), minimal fat angiomyolipoma (AML) and papillary RCC (pRCC) based on preoperative three-phase CT scans [60]. Feng et al. achieved an accuracy, sensitivity, specificity and AUC of 93.9%, 87.8%, 100% and 0.955, respectively, in discriminating small angiomyolipoma without visible fat from renal cell carcinoma (RCC) using CT texture analysis [61]. Eight machine learning algorithms was used in the study by Erdim et al., aiming at investigate whether machine learning-based CT texture analysis could distinguish benign and malignant renal solid masses [62]. The result showed that RAF algorithm achieved the best predictive performance based on five selected contrast-enhanced CT texture features, with an accuracy and AUC of 90.5% and 0.915, respectively. Yang et al. developed radiomics models based on image features extracted from unenhanced CT scan or different post-contrast enhanced scans to differentiate small (< 4 cm) renal angiomyolipoma without visible fat and RCC [63]. It was revealed that radiomics features extracted from unenhanced CT scan made a major contribution to the differentiation, providing the possibility of waiving the need for contrast-enhanced CT. The radiomics nomogram that combines the Rad-score and clinical factors showed a better discrimination capability compared with the clinical factors model in the discrimination of renal angiomyolipoma without visible fat from homogeneous ccRCC [64].

RCC nuclear grading is now widely accepted as has prognostic significance. Renal biopsy is still considered to be the golden standard for obtaining an accurate assessment of tumor pathological grade before surgery. Unfortunately, the application of renal biopsy has been extremely limited due to its invasive character,

Table 1. Published radiomics research in bladder cancer (BCa)

References	Nature of study	Application	Case numbers	Imaging modality	Results
Garapati et al. [29]	Retrospective	Tumor staging	76	CT	Four classifiers showed comparable results in BCa staging
Zhang et al. [30]	Retrospective	Tumor grading	61	MRI	MRI texture features extracted from DWI and ADC maps were able to distinguish low- and high-grade BCa
Wang et al. [31]	Retrospective	Tumor grading	70	MRI	Joint model constructed from T2WI, DWI and ADC performed best
Fan et al. [33]	Retrospective	Tumor differentiation	66	CT	Tumor heterogeneity extracted using GLCM and GLDM could separate MPC from UC
Zheng et al. [46]	Retrospective	Tumor differentiation	199	MRI	The radiomics-clinical nomogram shows favorable result in discriminating NMIBC from MIBC with an AUC of 0.922 in the training set
Xu et al. [47]	Retrospective	Tumor differentiation	68	MRI	MRI radiomic features achieved a result in differentiating between NMIBC and MIBC with the AUC of 0.8610
Tong et al. [48]	Retrospective	Tumor differentiation	65	MRI	T2-weighted MRI-based radiomics showed promising result in classifying BCa into different stage groups (non-muscle invasive vs muscle-invasive)
Wu et al. [54]	Retrospective	LN metastasis prediction	118	CT	CT-based radiomics nomogram could be used for prediction of LN metastasis in BCa
Wu et al. [55]	Retrospective	LN metastasis prediction	103	MRI	Radiomics nomogram based on MRI shows favorable predictive accuracy for LN metastasis in BCa
Xu et al. [56]	Retrospective	Recurrence stratification of BCa	71	MRI	The radiomic-clinical nomogram performed better than the radiomics or clinical model alone
Cha et al. [57]	Retrospective	Treatment response assessment	123	CT	Radiomics has the potential to aid in the evaluation of therapy responses

the metastatic potential along the needle path, the high risk of bleeding and puncture of the tumor, and the relatively low accuracy in assessing the tumor grade based on the biopsy. Recent studies have shown that machining learning-based CT texture analysis can accurately distinguish between high and low grades of RCC [65, 66]. MR-based texture analysis also demonstrated excellent diagnostic performance in differentiating high-grade from low-grade ccRCC [67]. Recently, studies have shown that the novel WHO/ISUP grading system is superior to the four-tiered Fuhrman grading system. The ISUP system can provide better grade separation, especially in grades 2 and 3 (a drawback in the Fuhrman system), and this new system has exhibited a stronger association with patient outcome [68, 69]. Shu et al. showed that machine learning-based CT radiomics analysis can be used for preoperative prediction of the WHO/ISUP grade of ccRCC [70]. The SVM model constructed using CT

radiomics features can effectively discriminate between high ISUP grade and low ISUP grade of ccRCC with an AUC of 0.88 and 0.91 in the training and validation set, respectively [71]. Cui et al. showed that MR-based radiomics models can serve as a noninvasive method for discriminating high ISUP grade from low ISUP grade of ccRCC, and mpMRI-based models may be superior to those based on single-sequence or single-phase imaging [72].

Radiogenomics is a field focusing on the association between a disease's imaging features and the underlying genetic patterns or molecular phenotype [73]. It establishes imaging biomarkers based on radiomics features to predict genomic profiles, which could potentially waive the need for invasive procedure. Kocak et al. adopted CT texture analysis based on unenhanced CT scan to evaluate the status of BAP1 mutations in ccRCC [74]. The RAF classifier achieved a precision of 81% for predicting ccRCCs with BAP1 mutation and a precision of 89.1% for predicting ccRCCs without BAP1 mutation. Interestingly, Feng et al. only used images in the CT enhancement nephrographic phase for construction of a radiomics model in order to predict BAP1 mutation status in patients with ccRCC [75]. The RAF model in the study achieved a precision of 0.65. Kocak et al. assessed the potential of CT texture analysis to predict the presence of PBRM1 mutations using artificial neural network (ANN) and RAF algorithms [76]. Finally, the ANN correctly classified 88.2% of ccRCC in terms of PBRM1 mutation status, while the RAF algorithm correctly classified 95% of ccRCC. Overall, the RAF classifer performed better than the ANN classifier. Application of radiomics in kidney cancer is summarized in **Table 2**.

Radiomics application in prostate cancer

Traditional diagnosis of prostate cancer (PCa) mainly relies on transrectal ultrasound (TRUS) guided biopsy. However, it involves substantial limitations including biopsy complications like bleeding and infection, low detection rate, overdiagnosis of clinically insignificant PCa while missing certain significant lesions [77-80]. There is an unmet need for non-invasive methods that predicting patients' cancer risk. For clinically significant PCa prediction, Li et al. developed three models, including a clinical model, a biparametric MRI (bp-MRI)-based radiomics model and a clinical-radiomics combined model [81]. The results revealed that both the MRI-based radiomics model and the clinical-radiomics combined model demonstrated better predictive efficacy than the clinical model. Xu et al. constructed a bp-MRI radiomics signature based on the six selected radiomics features of bp-MRI, which performed better than each single imaging modality including the T2-weighted imaging (T2WI), DWI and ADC imaging [82]. Whether men with a prostate-specific antigen (PSA) level of 4-10 ng/mL should receive a biopsy is still under debate. Qi et al. developed a combined model incorporating mp-MRI-based radiomics signature and clinical-radiological risk factors in patients with PSA levels of 4-10 ng/mL to make a preoperative prediction of prostate cancer (PCa) [83]. The combined model achieved an AUC of 0.956 and 0.933 in the primary and validation cohorts, respectively. Compared with the clinical-radiological model, the combined model showed better performance on both the primary and validation cohort.

Intra-tumoral heterogeneity may lead to the underperformance of the current pretreatment assessment of tumor stage [84]. Efforts have been made in order to improve staging accuracy. A radiomics signature based on 17 radiomics features from T2WI had the potential to predict status of extracapsular extension preoperatively, with an AUC of 0.902 and 0.883 in the training and validation cohort, respectively [85]. Stanzione et al. showed that ML method could predict histopathological extraprostatic extension of the PCa using texture features extracted from unenhanced MR images [86]. Gleason score (GS), which is often underestimated at the time of biopsy, has prognostic value. Thus, a non-invasive method to predict GS is of great value. Fehr et al. demonstrated that textural features from T2WI and ADC could show differences between Gleason 3+3 and higher Gleason scores (3+4 and 4+3 disease) [87]. Nketiah et al. have revealed that T2WI-derived textural features correlated significantly with GS and could differentiate GS 3+4 from 4+3 cancers [88]. GS is crucial for decision-making in PCa management. An accurate identification of the potential of upgrading in GS would minimize the possibility of undertreatment of PCa patients and provide more information in

Table 2. Published radiomics research in kidney cancer

References	Nature of study	Application	Case numbers	Imaging modality	Results
Yan et al. [60]	Retrospective	Tumor differentiation	50	CT	CT texture analysis was able to differentiate between ccRCC, minimal fat AML and pRCC
Feng et al. [61]	Retrospective	Tumor differentiation	58	CT	Machine-learning based texture analysis was able to differentiate small AML without visible fat from RCC
Erdim et al. [62]	Retrospective	Tumor differentiation	84	CT	RAF algorithm performed best in differentiating benign and malignant renal solid masses with an accuracy of 90.5%
Yang et al. [63]	Retrospective	Tumor differentiation	163	CT	Radiomics features extracted from unenhanced CT could differentiate small (< 4 cm) renal AML without visible fat and RCC
Nie et al. [64]	Retrospective	Tumor differentiation	99	CT	The radiomics nomogram showed a better capability compared with the clinical factors model in the discrimination of AML without visible fat from homogeneous ccRCC
Bektas et al. [65]	Retrospective	Tumor grading	54	CT	Texture analysis can accurately distinguish between high and low grades of RCC
Lin et al. [66]	Retrospective	Tumor grading	232	CT	Machine learning classifiers can noninvasively distinguish between high and low grades of RCC
Goyal et al. [67]	Retrospective	Tumor grading	34	MRI	MR-based texture analysis demonstrated excellent diagnostic performance in differentiating high-grade from low-grade ccRCC
Shu et al. [70]	Retrospective	Tumor grading	271	CT	Machine learning-based CT radiomics analysis can be used for preoperative prediction of the WHO/ISUP grade of ccRCC
Sun et al. [71]	Retrospective	Tumor grading	227	CT	The svm model based on CT radiomics features can effectively discriminate between high ISUP grade and low ISUP grade of ccRCC
Cui et al. [72]	Retrospective	Tumor grading	460	MRI	MR-based radiomics models can noninvasively discriminate high ISUP grade from low ISUP grade of ccRCC
Kocak et al. [74]	Retrospective	Radiogenomics	65	CT	The RAF classifier achieved a precision of 81% for predicting ccRCCs with BAP1 mutation and a precision of 89.1% for predicting ccRCCs without BAP1 mutation
Feng et al. [75]	Retrospective	Radiogenomics	54	CT	The RAF model based on CT enhancement nephrographic phase achieved a precision of 0.65 in predict BAP1 mutation status
Kocak et al. [76]	Retrospective	Radiogenomics	45	CT	The ANN correctly classified 88.2% of ccRCC in terms of PBRM1 mutation status, while the RAF algorithm correctly classified 95% of ccRCC

selecting patients fitable for active surveillance. Zhang et al. showed that mpMRI-based radiomics had the potential to predict upgrading of PCa from biopsy to radical prostatectomy (RP) [89]. The mode that combines the radiomics signature, clinical stage, and time from biopsy to RP demonstrated better performance than the clinical model and radiomics model, with an AUC of 0.910, 0.646 and 0.868, respectively. Gong et al. also showed that

radiomics based on bpMRI could noninvasively distinguish high-grade PCa from low-grade PCa preoperatively [90].

The value of radiomics on predicting treatment response has also been studied. T2-weighted Haralick features may be strongly associated with biochemical recurrence following prostate cancer radiotherapy [91]. Bourbonne et al. found that MRI ADC map-based radiomics model could serve as a strong predictor of biochemical recurrence (BCR) after RP. Compared to the clinical model (with an accuracy of 63%), the radiomics model achieved an accuracy of 78% and allowed for significant stratification of patients for biochemical recurrence-free survival [92]. Another study showed that radiomics features extracted from pretreatment bpMRI can predict PCa BCR after therapy and may identify patients who would benefit from adjuvant therapy [93]. Bourbonne et al. showed that one radiomics feature from ADC was predictive of BCR with an AUC of 0.79 while no clinical feature was correlated with BCR in the training set [94]. In the testing set, this feature remained predictive of BCR and BCR-free survival (bRFS) with an AUC of 0.76. Carbon ion radiotherapy (CIRT) is a promising radiotherapy technique, which offers biological and physical advantages over conventional photon radiotherapy as it allows for better tumor control while minimizing adjacent normal tissues affection [95]. However, the relatively high cost of CIRT would bring burden to many patients. Thus, a low-cost, non-invasive method to identify PCa patients who may benefit from CIRT before treatment would be of great clinical value. Wu et al. showed that radiomics features extracted from T2w and ADC images demonstrated high accuracy in predicting individualized treatment response of CIRT [95].

Radiogenomics has also gained popularity in PCa in recently years. One of the first radiogenomics study in PCa revealed that there existed a significant association between the quantitative dynamic contrast-enhanced MRI feature k(ep) and GS with PTEN expression in peripheral zone PCa [96]. Stoyanova et al. correlated 49 mp-MRI based radiomics features with three clinically available gene signatures associated with adverse outcome in PCa. The results showed that there were significant correlations between the radiomics features and these genes, indicating the prognostic value of radiomics features in PCa [97]. Fischer et al. identified four biomarkers (ANPEP, mir-217, mir-592, mir-6715b) that had the potential to distinguish between T2c stage and T3b stage [98]. The biomarkers were highly correlated with aggressiveness-related imaging features extracted from mp-MRI images. Application of radiomics in PCa is summarized in **Table 3**.

Radiomics application in testicular cancer

Testicular cancer is the most common malignant tumor among men aged between 14 and 44 years [99]. Radical orchiectomy remains the main treatment for testicular tumors and can be supplemented by radiotherapy and chemotherapy [100]. Considering the different sensitivities of seminomas and nonseminomas to radiotherapy and chemotherapy, it is necessary to distinguish these two tumors for patients who are unwilling to undergo orchiectomy. In view of the potential risk of biopsy including tumor spread and metastasis, a non-invasive method is of great need. Zhang et al. constructed a radiomics signature from five T2WI-MRI radiomics features. The radiomics signature can effectively discriminate between seminomas and nonseminomas with an AUC of 0.979 [100]. For patients with metastatic non-seminomatous testicular germ cell tumors, it would help patients avoid overtreatment if we can predict the presence of malignant histopathology in retroperitoneal lymph nodes metastases prior to lymph node dissection. Baessler et al. developed a CT-based radiomics machine learning classifier [101]. The classifier achieved a classification accuracy of 0.81 in the validation dataset while the model incorporating only the LN volume achieved a classification accuracy of 0.68. Another study showed that the accuracy of CT-based radiomics algorithm was 72% alone and was improved to 88% when combined with clinical predictors in predicting pathology of postchemotherapy retroperitoneal lymph node masses in metastatic testicular germ cell tumors [102]. Application of radiomics in testicular cancer is summarized in **Table 4**.

Challenges and future directions

Numerous studies have been carried out in illustrating the application of radiomics in almost every aspect of genitourinary tumors, especially in bladder cancer, kidney cancer and prostate cancer. Studies focusing on other tumors like renal pelvis cancer, ureter cancer and penis cancer are still very limited. Mp-MRI,

Table 3. Published radiomics research in prostate cancer (PCa)

References	Nature of study	Application	Case numbers	Imaging modality	Results
Li et al. [81]	Retrospective	Cancer risk prediction	381	MRI	Both the MRI-based radiomics model and the clinical-radiomics combined model performed better than the clinical model
Xu et al. [82]	Retrospective	Cancer risk prediction	331	MRI	Bp-MRI radiomics signature performed better than each single imaging modality including the T2WI, DWI, and ADC
Qi et al. [83]	Retrospective	Cancer risk prediction	199	MRI	The model that combines the mp-MRI radiomics signature and clinical-radiological risk factors achieved an AUC of 0.956 in the in the primary cohorts
Ma et al. [85]	Retrospective	Tumor staging	210	MRI	A radiomics signature based on 17 radiomics features from T2WI had the potential to predict status of extracapsular extension preoperatively
Stanzione et al. [86]	Retrospective	Tumor staging	39	MRI	Texture features extracted from unenhanced MR images could be used to predict histopathological extraprostatic extension of the PCa
Fehr et al. [87]	Retrospective	Cancer risk prediction	217	MRI	Textural features from T2WI and ADC could show differences between Gleason 3+3 and higher Gleason scores
Nketiah et al. [88]	Retrospective	Cancer risk prediction	23	MRI	T2WI-derived textural features correlated significantly with GS and could differentiate GS 3+4 from 4+3 cancers
Zhang et al. [89]	Retrospective	Tumor grading	166	MRI	mpMRI-based radiomics had the potential to predict upgrading of PCa from biopsy to radical RP
Gong et al. [90]	Retrospective	Tumor grading	489	MRI	Radiomics based on bpMRI could noninvasively distinguish high-grade PCa from low-grade PCa
Gnep et al. [91]	Retrospective	Treatment response	74	MRI	T2-weighted Haralick features may be strongly associated with BCR following prostate cancer radiotherapy
Bourbonne et al. [92]	Retrospective	Treatment response	195	MRI	MRI ADC map-based radiomics model could serve as a strong predictor of BCR after RP
Shiradkar et al. [93]	Retrospective	Treatment response	120	MRI	Radiomic features extracted from pretreatment bpMRI can predict PCa BCR after therapy
Bourbonne et al. [94]	Retrospective	Treatment response	107	MRI	Radiomics feature from ADC was predictive of BCR with an AUC of 0.79
Wu et al. [95]	Retrospective	Treatment response	23	MRI	Radiomics features extracted from T2w and ADC images demonstrated high accuracy in predicting individualized treatment response of CIRT
McCann et al. [96]	Retrospective	Radiogenomics	45	MRI	A significant association existed between the quantitative dynamic contrast-enhanced MRI feature k(ep) and GS with PTEN expression in peripheral zone PCa
Stoyanova et al. [97]	Retrospective	Radiogenomics	17	MRI	There were significant correlations between the radiomics features and genes
Fischer et al. [98]	Retrospective	Radiogenomics	298	MRI	Biomarkers were highly correlated with aggressiveness-related imaging features extracted from mp-MRI images

especially DWI, may have the potential to be used as a non-invasive method to quantitatively evaluate tumor grade and histologic subtyping in penis cancer, which lays a solid foundation for the application of radiomics [103]. We believe that recent years will see the growth of radiomics studies in these tumors.

However, there are significant issues concerning radiomics that need be to addressed when put in actual use. Radiomics requires the use of specialized software, which may lead to additional costs and training. Imaging acquisition, segmentation methods, reconstruction algorithms and radiomics analysis tools vary among centers and scanners. It has been reported that the analysis of signal in MR images is difficult to generalize due to the issue of normalization and regularization [20, 104]. Radiomics feature measurements could be influenced by factors like imaging acquisition, tumor volume and other pre-processing steps [15, 105, 106]. Thus, reproducibility of radiomic features should be tested in the workflow. Moreover, results from different studies might be difficult to compare due to the lack of standardized analysis method. As many studies are retrospective, the radiomics features extracted often far exceeds the number of patients. This may lead to a selection bias and a high false-positive result [107].

Table 4. Published radiomics research in testicular cancer

References	Nature of study	Application	Case numbers	Imaging modality	Results
Zhang et al. [100]	Retrospective	Tumor differentiation	39	MRI	Radiomics signature derived from MRI can effectively discriminate between seminomas and nonseminomas with an AUC of 0.979
Baessler et al. [101]	Retrospective	Tumor differentiation	80	CT	The CT-based radiomics machine learning classifier could predict the presence of malignant histopathology in retroperitoneal lymph nodes metastases
Lewin et al. [102]	Retrospective	LN metastasis prediction	77	CT	The accuracy of CT-based radiomics algorithm was improved to 88% when combined with clinical predictors in predicting pathology of postchemotherapy retroperitoneal lymph node masses in metastatic testicular germ cell tumors

Furthermore, large amounts of current studies are carried out in a single institution with a small sample size. Some studies lack external validation for radiomics model development. In the future, a well-designed multi-center prospective study with enough cases should be carried out to test the reliability and reproducibility of the radiomics model.

Further studies should focus on the combination of radiomics-based biomarkers with other non-imaging biomarkers as combined analysis of a panel of biomarkers is the most promising method that has the potential to change clinical management [108]. Radiogenomics combines genomics with radiomics and could potentially waive the need for invasive diagnostic procedures like biopsy. This could be a breakthrough point for future research.

In the future, with radiomics analysis, traditional imaging analysis, common sense and experience of experts all combined together, we may deliver state-of-the-art medical care that outperforms what either of them can achieve alone. With larger medical databases established and further development of artificial intelligence (AI) techniques developed, the improved algorithms may not only be performed on computer, but also be performed on mobile devices or by access to cloud services in a timely manner. It would bring great benefit to the overall management of diseases including tumors.

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Disclosure of conflict of interest

None.

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