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The Role of CT-Based Radiomics in Precise Imaging of Renal Cancer

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Abstract

The application of advanced computational analysis to medical imaging opens a plethora of opportunities in the field of radiology, allowing for more accurate tissue characterization and, eventually, advancing towards precision medicine through imaging biomarkers. In this review, we briefly introduce the methodology for radiomics analysis and the main challenges for implementation of radiomics-based tools in clinical practice. Based on systematic review of published studies, we also summarize here the main advances regarding CT-based radiomics applications in renal cancer with regards to tumor characterization (diagnosis, grading, prognosis), gene expression prediction (radiogenomics) and response evaluation.

General Introduction of Radiomics Analysis

Rapid CT image acquisition during various phases of contrast enhancement is routinely used as a non-invasive method of diagnosis and staging of renal tumors[1,2]. Radiological characteristics provide valuable information but are subject to the reader's image interpretation. Recently established, the field of quantitative imaging (radiomics) utilizes a large set of imaging features automatically computed from segmented volumes-of-interest (VOI) for building different diagnostic and prognostic models, which can surpass standard practice[3-5].

In the last two decades, the treatment landscape of renal cell carcinoma (RCC) has been revolutionized by developing novel therapeutic agents, now available in clinical practice. As a consequence, personalized care has become a critical part of developing effective treatment guidelines and improving patient outcomes. Emerging research reveals associations between radiomics features and gene expression, which potentiate identification of promising imaging markers for treatment response prediction[6-10].

Imaging modality and VOI definition

Radiomics can be applied to different medical imaging modalities, however, we focus on computed tomography (CT), by far the most extensively used imaging technique in clinical practice. It facilitates volumetric and longitudinal assessment of radiological tissue densities and provides information on tumor enhancement distribution after contrast application. Radiomics uses manual or (semi-)automatic VOI segmentation, which allows the analysis of the most informative location (usually encompassing the entire tumor volume), while tumor sub-volume (e.g., periphery) or healthy tissue could also be analyzed.

Feature extraction

To date, the most common radiomics models applied to the renal cancer field are based on pre-designed features (also referred to as hand-crafted or engineered features). Nevertheless, recent advancements in deep learning have caused trends towards deep learning-based radiomics, which are beyond the scope of this review.

Hand-crafted radiomics features allow quantification of different tissue characteristics, which can be divided into different classes, i.e., morphological features (shape-based) and first-order (histogram-based), and second order and higher order distribution (texture-based features). For instance, texture-based features are most frequently used in radiomics studies differentiating renal lesion subtypes[4, 5, 11].

Modelling

The number of hand-crafted radiomics features can be high (ranging from 4 to 18720[12]), which would result in an overfitted model with poor generalizability. Therefore, only a subset of extracted features is used to effectively build a radiomics model. This can be achieved with feature selection techniques that remove redundant, highly correlated features (e.g., based on correlation or clustering) and/or by selecting the most informative features based on the target outcome (e.g., Least Absolute Shrinkage and Selection Operator (LASSO) regression, Minimum Redundancy Maximum Relevance (mRMR) or decision trees). Features that are reproducible and robust against different sources of data variability related to image acquisition or VOI segmentation are usually selected using a correlation score, such as Concordance Correlation Coefficient (CCC) or Intraclass Correlation Coefficient (ICC).

Different models are employed in radiomics applications; the most popular include regression models, random forest (RF) and support vector machine (SVM). Multiple-model creation is desirable, but not essential, as long as the methodology is well-reported, available and can be easily reproduced. It is also crucial to evaluate the radiomics model performance using internal and ideally external validation. The model performance is typically measured using the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC), which allow quantification of the model sensitivity and specificity.

Application of CT-Based Radiomics Towards Improving Renal Cancer Care: Diagnosis, Prognosis and Prediction of Response

Applying CT-based radiomics towards improving renal cancer care has two main goals: to improve clinical practice by providing earlier, more accurate cancer diagnosis, and to refine patient stratification and treatment selection by applying novel prognostic and predictive imaging biomarkers. Addressing these clinical needs often requires histological analysis of tumor samples; this creates limitations such as potential complications from these invasive procedures, and the inability to capture tumor heterogeneity (as tumor samples represent only a small portion of tumors). CT-based radiomics analysis aims to provide non-invasive tools for histological differentiation, tumor grading and patient survival characterization.

A systematic review has been performed to find articles investigating CT-based radiomics analysis for RCC characterization, prognosis and response evaluation (more detailed methodology of the systematic review in Annex I). Articles were classified based on the three main applications: histopathology differentiation (Table 1), tumor grading (Table 2), genetic expression (Table 3), and prediction of response.

Tumor subtypes differentiation

CT-based radiomics studies in renal cancer have been mainly focused on differentiation of RCC subtypes (ccRCC, pRCC or chRCC) from benign tumors such as oncocytoma or angiomyolipoma[3, 13-18]. Renal tumors are widely heterogeneous and differentiating between rare tumor subtypes and benign tumors can be particularly challenging[19]. Therefore, the main objective of radiomics analysis in this application, besides the need of non-invasive techniques for tumor detection, is to provide support for differentiating the most complex subtypes. Radiomics-based biomarkers could be key support tools in medical decision-making, as different subtypes of RCC entail heterogeneous prognosis, genetic expression and response patterns to treatment. In this regard, Li[20] developed a CT-based radiomics multiphasic study for differentiating ccRCC (an aggressive cancer with poor outcome) from non-ccRCC. The CT-based radiomics signature was able to classify ccRCC from non-ccRCC with an accuracy of >90% in both training and validation cohorts. They also showed that the radiomics-phenotype correlated with the von Hippel-Lindau (VHL) gene mutation, a key ccRCC driver.

The diagnostic capabilities of radiomics for differentiating renal tumor subtypes were recently assessed in two meta-analyses including 10 and 30 studies and with Log Odds Ratio of 2.56 [95%-CI 2.01, 3.11] and 3.17 [95%-CI 2.73, 3.62], respectively[12, 21].

Tumor grading

Beyond RCC tumor subtype classification, tumor grading is a key factor to determine aggressiveness in ccRCC, the most common and lethal renal tumor[19]. In current clinical practice, tumor grade is assessed by histological hematoxylin and eosin (H&E) analysis of tumor biopsies. However, two grading systems have been defined and used in clinical practice and, therefore, also applied to radiomics modeling first, the Fuhrman grading system and later, the

Table 1. CT-based radiomics studies for tumor differentiation in Renal Cell Carcinoma (RCC).

Study	N	Tumor type	Treatment	Study type	Feature Selection	Model	Validation	Reproducibility
Yu H (2017)	119	RCC	NA	Retrospective	NA	SVM	internal	NA
Kunapuli G (2018)	150	RCC	Surgery	Retrospective	RFE/SVM	RFGB/RF	none	NA
Li ZC (2019)	170	RCC	NA	Retrospective	mRMR/RF	RF	external	ICC inter- and intra-observer (filtering ICC>0.85)
Sun XY (2020)	254	RCC	Surgery	Retrospective	RFE	SVM	internal	ICC Inter-observer (filtering ICC>0.9)
Li Y (2019)	61	RCC	Surgery	Retrospective	LASSO-logistic regression model	SVM	internal	NA
Ma Y (2020)	59	RCC	Surgery	Retrospective	ANOVA/Mann Whitney U test/ correlation test/ LASSO-logistic regression model	logistic regression model	internal	Inter-observer ICC range [0.796-0.939]
Uhlig J (2020)	94	RCC	Surgery	Retrospective	RFE	RF	internal	Inter- and intra- observer (mean 0.513 and 0.435, respectively)
Yap FY (2021)	735	RCC	Surgery	Retrospective	NA	AdaBoost RF	internal	Inter-observer (filtering ICC>0.80)

ANOVA: Analysis of Variance; ICC: Intraclass Correlation Coefficient; LASSO: Least Absolute Shrinkage and Selection Operator; mRMR: minimum Redundancy Maximum Relevance; RF: Random Forest; RFE: Recursive Feature Elimination; RFGB**:** Relational Functional Gradient Boosting; SVM: Support Vector Machine

Table 2. CT-based radiomics studies for predicting tumor grade in Renal Cell Carcinoma (RCC).

Study	N	Tumor type	Treatment	Study type	Feature Selection	Model	Validation	Reproducibility
Ding J (2018)	114	RCC	Surgery	Retrospective	LASSO-logistic regression model	multivariate logistic regression model	external	inter-observer
Shu J (2018)	260	RCC	NA	Retrospective	LASSO-logistic regression model	multivariate logistic regression model	none	Inter-observer (filtering ICC>0.80)
Gill TS (2019)	83	RCC	Surgery	Retrospective	Mann-Whitney U test	univariate logistic regression model	none	NA
He X (2019)	227	RCC	Surgery	Retrospective	LASSO-logistic regression model	LASSO-logistic regression model	none	NA
Sun X (2019)	227	RCC	Surgery	Retrospective	variance selection/ single variable selection/ LASSO	SVM	internal	Inter-observer (filtering ICC>0.75)
Kocak B (2019)	81	RCC	NA	Retrospective	univariate logistic regression	ANN / logistic regression	Internal	Inter-observer (filtering ICC>0.9)
Shu J (2019)	163	RCC	Surgery	Retrospective	LASSO-logistic regression model	KNN/ logistic regression model/ MLP/RF/ SVM	internal	Inter-observer (filtering ICC>0.8)
Nazari M (2020)	71	RCC	Surgery	Retrospective	LASSO-logistic regression model/ mRMR/T-test	multivariate logistic regression model/ SVM/RF	internal	NA
Zhou H (2020)	124	RCC	Surgery	Retrospective	MICI/RFE	RF	internal/ external	Inter-observer (filtering ICC>0.75)

ANN: Artificial Neural Network; ICC: Intraclass Correlation Coefficient; KNN: K-Nearest Neighbor; LASSO: Least Absolute Shrinkage and Selection Operator; MICI: maximizing independent classification information; MLP: multilayer perceptron; mRMR: minimum Redundancy Maximum Relevance; RF: Random Forest; RFE: Recursive Feature Elimination; SVM: Support Vector Machine

WHO/ISUP (International Society of Urological Pathology) grading system, the most generally adopted[22].

Different tumor grades involve distinct biological behaviors, accounting for risk of metastatic disease,

Table 3. CT-based radiomics studies for predicting tumoral gene expression in Renal Cell Carcinoma (RCC).

Study First Author (Year)	N	Tumor type	Treatment	Study type	Outcome	Feature Selection	Model	Validation	Reproducibility
Ghosh P (2015)	78	RCC	NA	Retrospective	BAP1	Mann-Whitney U test	RF	internal	NA
Kocak B (2020)	65	RCC	NA	Retrospective	BAP1	Pearson correlation/ wrapper-based classifier-specific algorithm	RF	internal	Inter-observer (filtering ICC>0.9)
Feng Z (2020)	54	RCC	Surgery	Retrospective	BAP1	Mann-Whitney U test/ Spearman Correlation	RF	internal	Inter-observer (filtering ICC>0.85)
Kocak B (2019)	45	RCC	NA	Retrospective	PBRM1	wrapper-based classifier-specific algorithm	ANN/RF	internal	Inter-observer (filtering ICC>0.90)
Chen X (2018)	57	RCC	NA	Retrospective	VHL PBRM1 BAP1	MCMO	MCMO	internal	NA

ANN: Artificial Neural Network; ICC: Intraclass Correlation Coefficient; MCMO: Multi-Classifier Multi-Objective; RF: Random Forest

survival and response to targeted therapies. Most of the studies focused on radiomics models for predicting tumor grade have used a dichotomous classification of low grade (I-II) (i.e., better prognosis) vs high grade (III-IV) (i.e., poorer prognosis)[23-32].

Gene expression studies

With the development of high-throughput methods to extract and correlate multiple imaging parameters with genomics data, a new opportunity in medical research has also emerged. Radiogenomics aims to correlate imaging features (i.e., the imaging phenotype) with gene expression patterns, gene mutations, and other genome-related data. The most commonly mutated genes in RCC are VHL, BAP1, PBRM1, SETD2 and KDM5C. Several groups have investigated the association between radiomics signatures and mutations of VHL tumor suppressor genes[8, 20, 33], the most frequent in ccRCC (80-90% of cases)[34]. However, a recent meta-analysis showed no prognostic value of VHL[35]. Since then, further radiomics studies in renal cancer have focused on PBRM1 and BAP1 mutation prediction[6-10], which have shown associations with clinical outcome[36]. Ghosh[6] model classified BAP1 mutational status with moderate area (AUC) between 0.55 and 0.70. While Feng[9] and Kocak[10], improved classification capacity to an AUC of 0.77 and 0.99, respectively. Moreover, Kocak[7] developed a radiomics signature capable of classifying 95% of PBRM1 mutated samples of ccRCC. Chen[8] applied a novel modeling technique which achieved validation accuracies between 85 and 93% for VHL, PBRM1 and BAP1 mutation prediction. Recently, Greco has shown an association between visceral adipose tissue (quantified in CT images) and KDM5C mutation, which could provide new prognostic information[33].

Treatment response assessment

Scarce data is currently available about CT-based radiomics for predicting response to different treatments. Mühlbauer reported only six studies investigating quantitative imaging for predicting response to systemic therapy[21], of which only two applied CT-based radiomics to predict response to anti-angiogenic treatment with limited data on radiomics model accuracy[37, 38]. Both articles implemented a univariate radiomics Cox regression model rather than combining different radiomics features in a multivariate predictive model. However, both studies analyzed changes between baseline and after administration of tyrosine kinase inhibitors (TKIs). Haider[38] found two radiomics features (entropy and size normalized standard deviation) significantly associated with survival at baseline. Goh[37] found that texture uniformity at baseline could predict the time to progression. Although some groups have shown promising results regarding the role of CT-based radiomics models for predicting response to immune checkpoint inhibitors (including a few RCC patients[39, 40]), limited data is available in exclusive RCC cohorts[41].

Challenges in Radiomics

Despite some promising results, the utility of radiomics models has not yet been translated into clinical practice due to several challenges.

Radiomics Quality Score (RQS) has been proposed as a standardized tool to assess the scientific integrity and the clinical relevance of radiomics studies by evaluating the key challenges in radiomics analysis[42]. Over the last three years, a few systematic reviews assessing the RQS of radiomics studies in renal cancer have been published[12, 21, 43] showing a rather low quality of radiomics studies (RQS from 9.4% to 33.3%). Of note, the key identified deficiencies were related to standardization, independent validation, cost effectiveness and open science data sharing. Nevertheless, the RQS has increased in more recent publications, suggesting that radiomics research is improving.

In principle, radiomics analysis begins with the target outcome definition, most commonly searching for novel imaging biomarkers. In practice, this decision is largely based on available imaging data, which could be obtained directly at the institution, together with collaborators or downloaded from open science databases such as The Cancer Genome Atlas (TCGA). Most published studies rely on retrospective data, which include technically variable data, for instance, due to diverse imaging protocols, scanners, vendors and even variable segmentations, which have been shown to affect the reproducibility of radiomics features[44-47]. This prompts the necessity for data harmonization and standardization. Prospective data collection allows for standardized imaging protocol design improving radiomics reproducibility and comparability but comes with its own disadvantages of being time consuming, prone to selection bias and consequently leading to low patient numbers. Recently published consensus suggests developing radiomics signatures on datasets representing realistic diversity in disease and acquisition protocols, such as in retrospective cohorts, and validating them in prospective trials[48]. Large and independent study cohorts are needed not only for model creation, but also for validation, reducing the risk of over-estimated model performance.

In the search for large and high-quality data substantial efforts are required to develop infrastructures to share, store and curate patient data. Multi-centric trials require secure platforms, and the ability to communicate between institutional networks. The economic potential of introducing radiomics in clinical practice could be estimated by assessing the cost per quality-adjusted-life-year[42, 49], which currently remains unclear.

Clinical translation of radiomics needs acceptance from both the scientific and clinical communities, which requires replicability of the proposed tool in independent institutions. This can only be achieved when sufficient information and data is available to reproduce the model in an independent setting. Therefore, radiomics results should be supported by the thorough description of all methodological steps. Although there is currently no gold-standard, standardization procedures for image processing and feature extraction were recently proposed by a large multi-center initiative[50]. Moreover, open science model and code sharing is highly recommended to facilitate replicability and contribute to the prompt progress in the field.

Conclusions

Although medical imaging has been the foundation of renal tumor detection and follow-up for decades, to date, observer-dependent evaluation has been a constraint of accurate tumor characterization and imaging biomarker development towards precision medicine. Nevertheless, advances in computational medical image analysis allow for large- and small-scale tumor feature quantification using automatically extracted data characterization algorithms (radiomics). Radiomics features provide substantial amount of information about the tumor intensity, shape and texture. The application of machine learning analysis to radiomics facilitates the identification of underlying imaging patterns that may be, otherwise, not obvious, providing an excellent tool for improved imaging data interpretation and biomarker development. In particular, radiomics analysis of multi-phase CT, the most extensively used imaging technique for renal cancer diagnosis and follow-up, offers enormous promise as an excellent alternative for accurate, safe, and non-invasive renal cancer characterization. As a matter of fact, dozens of studies on CT-based radiomics applications in renal cancer have been published over the last decade. In this review we have summarized the main studies in this regard.

Most of the research on radiomics-based models applied to renal cancer has been focused on lesion characterization (benign vs malignant) and tumor grading. Although still scarce, a few studies have also shown promising results regarding the role of CT-based radiomics in treatment selection. Moreover, accounting for the high spatial and temporal heterogeneity of renal tumor, CT-based radiogenomics have great potential to facilitate a deeper understanding of tumor biology, as Li[20] demonstrated by correlating a CT-based radiomics phenotype with Von-Hippel Lindau gene mutation.

Despite the considerable excitement resulting from the first ever studies in radiomics, there remains an awareness of its flaws in reproducibility, largely due to the variety of image acquisition and processing protocols. Different approaches have been considered in order to ameliorate radiomics variability, such as, non-reproducible radiomics feature filtering or the application of post-image acquisition correction models. These methods expand the potential of CT-based radiomics implementation in retrospective and prospective multi-center large-scale studies, allowing for achieving meaningful generalizable CT-based radiomics assays for supporting medical decisions in clinical practice. Moreover, the lack of adherence to the standardized radiomics analysis methods defined by the image biomarker standardization initiative (IBSI)[50] has precluded generalization and clinical qualification of radiomics-based biomarkers also in renal cancer.

All in all, although the field of radiomics is still in its infancy and continuously evolving, some of the studies presented here show promising applications of radiomics analysis towards a more precise and earlier renal cancer detection, tumor characterization, patient stratification and treatment selection. Furthermore, integrating radiomics

with clinical, molecular and genomic data may allow successful design of even more accurate models. Despite further prospective studies being needed to validate and clinically qualify these novel biomarkers, precise radiomics quantification opens a new paradigm in medical imaging interpretation and exploitation, likely providing new tools to support medical decisions and, ultimately, improving renal cancer patient care.

Supplementary I: Systematic Review

The systematic review was performed following the PRISMA guidelines[51]. PubMed electronic database was searched from January 1st, 2014 to May 1st, 2021 for original English articles investigating CT-based radiomics analysis in cancer applications with the search term (radiomics OR radiogenomics) AND (CT NOT PET) AND (Tumor OR Cancer OR Oncology). This search was performed using the new and the legacy version of PubMed. Both searches have been merged afterwards to include the maximum number of articles. The resulting database was filtered by renal cell carcinoma (RCC). The included original studies met the PICOS criteria[51]: Population – treated patients with cancer and including N>20, Intervention – CT-radiomics analysis, Control – standard of care, Outcome– cancer diagnosis, prognosis or prediction, Study design – Retrospective and prospective observational studies. One article was excluded because the number of patients was lower than 20; 4 articles were using qualitative features instead of quantitative engineered features; 1 did not implement machine learning algorithms and 2 were reviews.

Conflicts of Interest Statement

The authors declare no competing interests.

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