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GYNECOLOGIC CANCERS (NS REED, SECTION EDITOR)

Radiomics: an Introductory Guide to What It May Foretell

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Abstract

Purpose of Review To briefly review the radiomics concept, its applications, and challenges in oncology in the era of precision medicine.

Recent Findings Over the last 5 years, more than 500 studies have evaluated the role of radiomics to predict tumor diagnosis, genetic pattern, tumor response to therapy, and survival in multiple cancers. This new post-processing method is aimed at extracting multiple quantitative features from the image and converting them into mineable data.

Summary Radiomics models developed have shown promising results and may play a role in the near future in the daily patient management especially to assess tumor heterogeneity acting as a whole tumor virtual biopsy. For now, radiomics is limited by its lack of standardization; future challenges will be to provide robust and reproducible metrics extracted from large multicenter databases.

Keywords Cancer · Radiomics · Texture · MRI · CT · PET/CT

Introduction

On a routine basis, as radiologists, we subjectively evaluate cross-sectional images from CT or MRI images based on our training and experience to provide a diagnosis or a response to treatment evaluation. Tools for more automated imaging analyses have been evaluated to decrease the inter-observer variability and provide more objective information [1, 2]. In the meantime, the role of CT or MRI in cancer evaluation is evolving from a purely diagnostic tool to a predictive role in the era of precision medicine. Indeed, describing the tumor and its extension is not sufficient when challenged regarding which treatment to give or evaluating early response to treatment [3, 4].

As part of new imaging development, radiomics has been introduced as a post-processing computational method linking qualitative and/or qualitative imaging data to clinical endpoints [5–9]. The term radiomics has been defined as "high-throughput extraction of quantitative features that results in the conversion of images into mineable data". The term radiogenomics links imaging features with genomic data for the same purpose [10–14]. The process used in radiomics involves the extraction, analysis, and interpretation of multiple quantitative features from medical images such as CT, MR, and/or PET, leading to a large volume of data that can be correlated with tumor diagnosis, genomics and/or prognosis [15–27]. Radiomics features (such as intensity, homogeneity, shape, or texture) offer information on cancer phenotype and genotype. Radiomics has already demonstrated considerable potential in neuroradiology for lesion characterization [6, 28–30]. In kidney cancer, for example, radiomics data such as entropy and standard deviation were correlated with aggressive tumor features such as histologic subtype and nuclear grade [31, 32]. Besides its correlation with histopathology, radiomics evaluation may also serve as a prognostic biomarker [33]. Moving forward, we are now at the era of worldwide databases that link immense volumes of radiomics data from millions of patients to create a large learning healthcare networks. The principal challenge is the optimal collection and

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integration of those data sets to deliver accurate, robust, and standardized models linked with clinical outcome.

In this short review, we will describe the radiomics evaluation along with its latest applications.

The Process of Radiomics

Radiomics analyses begin with the choice of a volume or area of interest on imaging and a prediction target. Typically, the entire primary tumor or tumor burden in case of metastatic disease is analyzed and linked to clinical data. Each tumor part can be segmented on any modalities (CT, MRI, PET) [2].

Radiomics evaluation is still on the research level and not available for routine clinical practice. It requires either an in-house developed software or one commercially available. Several software are available as open source on the Internet. Radiomics can be performed retrospectively and divided in several steps [34, 35] (Fig. 1):

- Image acquisition: Image acquisition can be performed either on MRI, CT, or PET scanner. One major challenge is the large variability in image acquisition parameters such as slice thickness, voxel size, and radiation dose. Sole robust features must be extracted.
- Image segmentation: Region of interest (ROI) or volume of interest (VOI) is usually manually or semi-automatically segmented and features are extracted. Careful choice of the ROI or VOI must be performed. Non-lesion/tumor part must be excluded as it influences the quantification of the subsequent features [36].
- Feature extraction: Different methods can be used to extract the considerable amount of data from the image (morphological, statistical, deep learning, etc.) [37]:

(a) Morphological features: Morphological features include features defining the physical characteristics of the tumor such a shape, sphericity, and roundness.

(b) Statistical features: First-order statistics are related to the frequency distribution of the pixel intensity inside the ROI called as well as intensity histogram. It includes common statistics such as mean, standard deviation, variance, skewness, etc.

Second-order statistics evaluate the spatial relationships between pixels. They are extracted from matrices such as co-occurrence matrices (e.g., Gray level co-occurrence matrix (GLCM)) [38••]. Those matrices investigate the relationship between a pixel with a certain gray level with the adjacent pixel of another gray level in the whole ROI and for all the pixels [34]. Texture features computed from the GLCM consist of energy, entropy, homogeneity, and contrast.

Third- and higher-order statistics evaluate the location and relationships between three or more pixels and evaluate features such as contrast, coarseness, and busyness.

One of the concerns of the statistical method is overfitting. Many of the features are correlated together; feature reduction techniques must be used in order to improve the model accuracy such as multivariate wrapper techniques, recursive feature elimination, and least absolute shrinkage and selection operator (LASSO) [39, 40].

(c) Deep learning: The statistical method corresponds to the use of features sets extracted and chosen by the reader which introduce as such some variability. Deep learning method is a more automated method with can avoid these limitations. Deep learning method does not require accurate segmentation as it automatically creates its own features through multiple layers of learning.

- Analysis: Not all of the features, however, are useful as some of them might be highly correlated with each other or redundant. Feature selection is used to select the “effective” features which are relevant. Traditional feature selection method includes univariate and multivariate analyses.

  The minimum redundancy maximum relevance (mRMR) is the most used feature selection method. Mutual information between a set of features and a predictor variable is calculated. Recently, new methods are emerging. RELIEF (RELevance In Estimating Features) has been investigated [41]. RELIEF evaluates interdependent features and has shown higher prediction accuracy compared with other methods [42]. FAST (Feature Assessment by Sliding Thresholds) corresponds to another feature ranking method which has the ability to decrease the effects of small sample size and imbalanced data problems [41, 42].

The Latest Development in Radiomics

Recent Advances in Radiomics and Radiogenomics

When performing a PubMed research over the last 5 years on radiomics, more than 500 studies have been published. Radiomics algorithm have been created and tested to predict tumor diagnosis, genetic pattern, tumor response to therapy, and survival in multiple cancers [43–47]. In this section, we will briefly review some of the recent results obtained with radiomics according to the type of cancer.

- Glioblastoma: Extensive work has been performed on radiomics and glioblastomas [48]. Recently, 11 radiomics

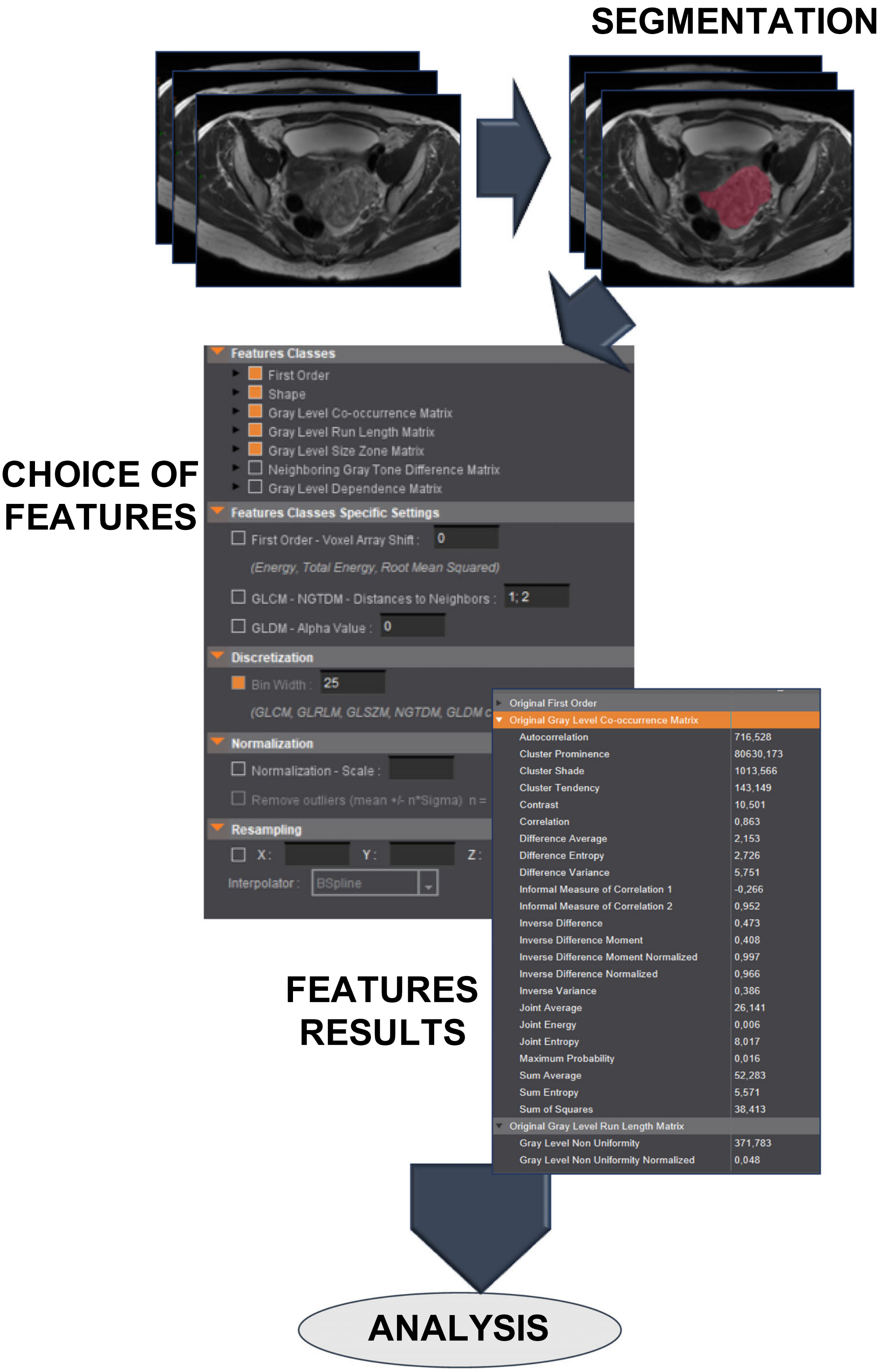

Fig. 1 Drawing summarizing the radiomics process from lesion segmentation to features extraction using a commercially available software for example here Olea Medical, La Ciotat, France

Features Classes
- ☑ First Order
- ☑ Shape
- ☑ Gray Level Co-occurrence Matrix
- ☑ Gray Level Run Length Matrix
- ☑ Gray Level Size Zone Matrix
- ☐ Neighboring Gray Tone Difference Matrix
- ☐ Gray Level Dependence Matrix

Features Classes Specific Settings

☐ First Order - Voxel Array Shift : 0

(Energy, Total Energy, Root Mean Squared)

☐ GLCM - NGTDM - Distances to Neighbors : 1; 2

☐ GLDM - Alpha Value : 0

Discretization

☑ Bin Width : 25

(GLCM, GLRLM, GLSZM, NGTDM, GLDM c

Normalization

☐ Normalization - Scale :

☐ Remove outliers (mean +/- n*Sigma) n =

Resampling

☐ X: Y: Z:

Interpolator : BSpline

Original First Order	
Original Gray Level Co-occurrence Matrix	
Autocorrelation	716,528
Cluster Prominence	80630,173
Cluster Shade	1013,566
Cluster Tendency	143,149
Contrast	10,501
Correlation	0,863
Difference Average	2,153
Difference Entropy	2,726
Difference Variance	5,751
Informal Measure of Correlation 1	-0,266
Informal Measure of Correlation 2	0,952
Inverse Difference	0,473
Inverse Difference Moment	0,408
Inverse Difference Moment Normalized	0,997
Inverse Difference Normalized	0,966
Inverse Variance	0,386
Joint Average	26,141
Joint Energy	0,006
Joint Entropy	8,017
Maximum Probability	0,016
Sum Average	52,283
Sum Entropy	5,571
Sum of Squares	38,413
Original Gray Level Run Length Matrix	
Gray Level Non Uniformity	371,783
Gray Level Non Uniformity Normalized	0,048

features extracted from multiparametric MRI were identified to stratify patients with newly diagnosed GBM into poor and good prognosis tumors in terms of outcome. Standard deviation of energy and gray level run emphasis were significantly correlated with patient prognosis. The performance of the models was higher compared to the radiologic and clinical risk models. Interestingly, the results were further improved when combining radiomics with clinical data [49]. Similarly, another radiomics prediction model demonstrated promising results when integrated with clinical and genetic profiles to improve prediction of survival [50]. Regarding tumor recurrence, it is well known that most of GBMs recur locally in the peritumoral area. A preliminary study has shown that MRI radiomics features related to heterogeneity originating from the peritumoral brain area were significantly associated with survival [51].

- Head and neck tumor: Similarly to GBM, radiomics has been applied to head and neck tumors. In a cohort of 127 patients, it was recently demonstrated that MRI radiomics signature could discriminate stages I–II from stages III–IV head and neck squamous cell carcinoma and may serve as a complementary tool for preoperative staging [52]. Regarding tumor response assessment, several studies have shown that pretreatment radiomics features may predict patient prognosis in nasopharyngeal carcinoma [53–55].
- Lung cancer: It is known that the discrimination between the invasive and non-invasive components is challenging in ground glass opacity lesions due to limited visual perception and subjective analysis of CT scans [56, 57]. Studies have shown that quantitative radiomics features of ground glass opacity lesions can help find small pathologically invasive components [58–60]. Radiomics features have also shown favorable results when linked to underlying genomic alterations in lung cancer. In a study including 285 patients, CT features were associated with alterations of EGFR (air bronchogram, pleural retraction, small lesion size, absence of fibrosis), ALK (pleural effusion), and KRAS (round lesion shape, nodules in non-tumor lobes) mutation [61]. In contrast, no specific features were found to be associated with BRAF-mutated lung cancer [62]. A data set of non-small cell lung cancer patient has been recently been created to facilitate the discovery of underlying relationship between tumor molecular alteration and imaging features [63]. Regarding prognosis, several radiomics models comprised of size, intensity, shape, texture, and wavelet features have shown to be associated with lung cancer prognosis, stage and histology [64, 65], and distant metastasis [66].
- Breast: Tremendous work has been performed in breast radiomics. Recent studies have shown that radiomics phenotypes can capture mammographic parenchymal complexity beyond conventional breast density and establish breast cancer risk factors. Indeed in a study including 2029 patients, the authors found that radiomics phenotypes of breast density were significantly associated with breast cancer [67]. Radiomics may also predict response to neoadjuvant chemotherapy. The analysis of dynamic contrast enhanced-MRI-based radiomics features on precontrast data was associated with tumor response to neoadjuvant chemotherapy [68]. Radiomics model of biopsy-proven breast cancers from the National Cancer Institute's multi-institutional Cancer Genome Atlas (TCGA) has shown to accurately predict the expression of ER, PR, HER, and triple negative [46]. The risk of recurrence as predicted from multigene assays (MammaPrint, Oncotype DZn and PAM50 gene assays) was investigated using a data set of 84 breast MRI from the National Cancer Institute Cancer Imaging Archive. Radiomics classifiers developed using logistic regression were predictive for the risk of recurrence of breast cancer [69].
- Prostate: Preliminary work has been performed on prostate cancer. In a recent study, the authors evaluated whether radiomics could help improve the performance of PIRADS v2 in clinically relevant prostate cancer (PCa). When radiomics was added, performance of PI-RADS v2 was significantly improved for PCa versus PZ (Az 0.983 (0.960–0.995)) and PCa versus TZ (Az 0.968 (0.940–0.985)) [9]. Additionally, radiomics features have shown associations with Gleason score. Nketiah et al. demonstrated that T2W textural features were able to differentiate Gleason 3 + 4 from Gleason 4 + 3 tumor [70]. In a study, Fehr et al., find differences between Gleason 3 + 3 and higher Gleason scores (3 + 4 and 4 + 3 disease) using textural features from T2W and ADC alone [71].
- Renal cell carcinoma: Work on mutational status of renal cell carcinoma has highlighted the genomic heterogeneity of the disease. Among those genomic alterations, clear cell renal cell carcinoma (RCC) has been divided into two subtypes (ccA/ccB). This classification has been proven to be a robust predictor for localized and metastatic tumors in which the ccB type is known to have worse prognosis. In a recent study using PET/MRI, a radiomics model had a correct classification rate for molecular subtype classification of 86.96%. When combined with mRNA, microvascular density, and clinical parameters, the model reached a correct classification rate of 95.65%. Those results are highly promising in terms of disease risk stratification and guidance of treatment in patients with primary ccRCC [72]. Regarding response to therapy, a study has evaluated the feasibility for performing radiomics analysis on PET/MRI to characterize early treatment response in metastatic RCC undergoing anti-angiogenic therapy (sunitinib). The authors found robust and reproducible radiomics features which could help predicting early response to treatment [73].
- Liver and pancreatic tumors: Similarly to other organs, radiomics models have been evaluated for liver and pancreatic tumors. For example, response to treatment in liver metastases has been evaluated. In a recent study, the CT radiomics approach showed potential in discriminating responding from non-responding liver metastases based on the pretreatment CT scan [74]. Several radiomics models have shown promising results in

assessment of tumor grade and presence of microvascular invasion [75–77]. Recently, the risk of cancer development in pancreatic IPMN has been evaluated. In a study including 103 patients, the radiomics model achieved an area under the receiver operating characteristic curve (AUC) of 0.77 when used alone and 0.81 when combined with clinical variables to predict the risk of IPMN. Development of such a preoperative model to discriminate between low-risk and high-risk IPMN may improve surgical decision-making [78].

- Colorectal: A radiomics model was recently developed and validated to be a significant predictor for discrimination of stages I–II from III–IV colorectal carcinoma with an AUC of 0.79 [47]. Other models have also been used to assess tumor grade and predict outcome [79]. A radiomics model for preoperative prediction of lymph node metastasis in patients with colorectal cancer (CRC) has been evaluated [80]. The model consisted of 24 features and showed a good discrimination, with a C-index of 0.736 [80]. In rectal cancer, T2W MRI-based radiomics features extracted from the whole tumor volume have been shown to outperform the combination of T2W and diffusion-weighted images in the assessment of complete response [33]. Similar results have confirmed those findings more recently [81].
- Gynecological tumors: A study of 41 patients evaluated a radiomics model to distinguish leiomyosarcoma (LMS) from atypical leiomyoma (ALM). Sixteen texture features differed significantly between LMS and ALM (*p* values < 0.001–0.036). The model achieved an accuracy of 0.75 [18]. In 137 women with endometrial cancer, a radiomics model achieved an AUC of 0.84 in predicting deep myometrial invasion, 0.80 for lymphovascular invasion, and 0.83 for predicting high-grade tumor [27]. In cervical cancers, models have evaluated the risk of tumor recurrence [82, 83]. For example, in one study, pre- and mid-treatment radiomics analysis was able to differentiate between good and poor responders with AUC ranging from 0.742 to 0.850 [83].

A Step Forward, Radiomics as Virtual Biopsy

Cancer cells demonstrate a high level of variability, even in different regions of the same tumor, between metastatic sites within the same patient and between patients. This high genetic variability can explain the failure of targeted therapies and let resistant clones emerge and proliferate. In this setting, techniques to quantify this inter- and intratumoral heterogeneity in cancer patients are critically needed as they may help guide treatment adaptation. As a non-invasive technique, radiomics is particularly interesting since it is not possible to biopsy every part of each tumor at multiple time points. In this setting, radiomics play a potentially important role. For example, in ovarian cancer, recent advances have shown that ovarian cancers have substantial molecular heterogeneity at presentation which may explain drug resistance [3, 84–88]. Studies have shown that wide inter-tumoral heterogeneity exists at the genomic level between primary OC and peritoneal implants [89–95]. Performing biopsies on each implant is not possible; however, getting a road map of the heterogeneity of the disease would be helpful to predict drug resistance and outcome. Recently, Vargas et al. developed a radiomics model to evaluate spatial heterogeneity between tumor implants in high-grade serous ovarian cancer on CT [96••]. The authors found that radiomics metrics evaluating texture dissimilarities were associated with poorer prognosis (inter-site similarity entropy, similarity level cluster shade, and inter-site similarity level cluster prominence; $p \leq 0.05$) and incomplete surgical resection (similarity level cluster shade, inter-site similarity level cluster prominence, and inter-site cluster variance) [2, 96••]. Similarly, Rizzo et al. evaluated in 101 patients with HGSOC whether CT radiomics features of ovarian masses were associated with incomplete surgical resection and were able to predict patient outcome [97]. The authors found that radiomics parameters related to mass size, homogeneity, and randomness were associated with residual tumor.

Artificial Intelligence and Radiomics

We can postulate that in the near future, with the development of artificial intelligence, software will automatically identify, segment, and extract features from the whole tumor burden to improve patient management. Such capabilities are on the technological, scientific, and clinical horizons. Additionally, the advances in data-sharing technology, which transcends institutional and national boundaries, will help collect large cohort of patients to improve radiomics robustness and reproducibility.

Challenges of Radiomics

Radiomics is a promising emergent tool but its implementation in clinical practice will require each step to be standardized and validated [98].

Currently, most of the published studies are from a single center with a variable number of patients and a wide range of methodology. Indeed, each step of the radiomics process varies widely across studies, making the comparison and reproducibility of the results challenging [36]. To overcome these limitations, an international committee of expert has published guidelines regarding definitions and recommendations for methods used in radiomics studies [99••]. There is indeed an urgent need for a standardization in the evaluation criteria and reporting guidelines in order for radiomics to develop. A radiomics quality score (RQS) has been developed to evaluate the quality of both past and future radiomics studies and to assess whether the study is compliant with best-practice procedures [100]. In this same setting, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) initiative has been performed [101]. Within this initiative, different recommendations were proposed especially in terms of prediction model validation, regardless of whether the model serves diagnostic or prognostic purposes.

Conclusion

Although many issues need to be addressed, radiomics raises hope as a tool to better predict tumor aggressiveness and response to therapy in oncology. Radiomics is leading a new way in the radiology field by moving the radiologist from his traditional visual analysis to a more objective quantitative setting. As such, the role of the radiologist is evolving. The radiologist may become the "computational specialist of medical imaging data" integrating imaging biomarkers automatically derived from imaging data to clinical data and decision-making.

Compliance With Ethical Standards

Conflict of Interest The authors declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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