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Application of Radiomics in Radiotherapy: Challenges and Future Prospects

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ABSTRACT

Background and Objective: Specific treatment for each patient based on their clinical data is one of the medical prospects of the future. Using data mining and machine learning techniques based on computer science in extracting the quantitative features of an image to improve the process of diagnosis, prognosis, prediction and response to cancer treatment is known as radiomics. This article examines the workflow, findings, challenges ahead, and the role of radiomics in precision medicine and individual therapy.

Methods: In this review article, we searched well-known indexes such as ISC, web of science, Google Scholar, Scopus, PubMed without time limit and based on the keywords radiomics, radiotherapy, cancer and quantitative imaging and relevant articles were collected.

Findings: Radiomics is a combination of everyday computer-aided diagnosis, machine learning methods, deep learning and human skills that can be used for quantitative description of the phenotypes of cancerous tumors. Image collection and processing, tumor segmentation, extraction of features, processing and modeling are some of the basic steps of the process of radiomics. Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound (US) methods are among the used images.

Conclusion: According to the results of this study, the prerequisite for the clinical implementation of radiomics is the elimination of deficiencies such as the dependence of the features on the imaging parameters, and the unrepeatability of the features. Therefore, a comprehensive approach should be adopted, stable and reproducible patterns should be developed to accept radiomics as a clinical prognostic tool.

Keywords: *Radiomics, Radiotherapy, Cancer, Quantitative Imaging*.

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Introduction

Cancer is now the third leading cause of death in Iran and is expected to become the leading cause of death in the next few years according to the current trend (1). Therefore, early detection and optimal and low-cost cancer treatment processes are of particular importance. Radiomics, which was first introduced in 2012, is a new knowledge based on image processing that examines many quantitative features of the image and their relationship with clinical metrics (2). Since then, computer scientists, diagnostic radiologists, and oncologists have turned to this new tool, using advanced methods to extract the information in the images. Researchers have developed and validated radiographic patterns based on new imaging and computational technologies that may improve the accuracy of diagnoses and the evaluation of therapeutic responses. Predicting response to treatment, prognosis, predicting overall survival and progression-free survival, diagnosing tumor homogeneity, distinguishing between malignant and healthy tissues, are some of the applications of this knowledge as image-based biomarkers in the treatment of cancer (3, 4).

Traditionally, the physician interprets the image by observation and based on previous learning and experience. There are exceptions though; for example, in nuclear medicine, where local metabolic activity can be quantified as a standard uptake value (SUV), recognizing and describing the location, intensity, shape, and clarity of an object and its consequences are subjective. Today, these interpretations are important for disease management. However, except in some cases, this is a mental task with variable sensitivity and specificity and great diversity among physicians (5).

Standard methods for identifying and describing cancerous tumors after initial laboratory tests and appearing in the image are based on genetic and pathological factors through tissue sampling. Genetic and histopathological biopsies and examinations can identify types of cancerous tumors and provide more data, but they have drawbacks. Most tumors are heterogeneous in terms of spatiotemporal patterns due to irregularities in metabolism, arteries, oxygen delivery, and gene expression, leading to multiple biopsies and additional damage to the patient. Under these circumstances, the use of advanced medical imaging to complement traditional diagnostic methods leads to a better evaluation of spatiotemporal dynamics of tumors. Therefore, due to its non-invasive nature, availability and its application in diagnosing and predicting the patient's prognosis, a new and special approach to medical imaging has been developed (6).

The information obtained from the image can be combined with other emerging medical analyses that are more commonly referred to with the suffix "omics", such as genomics, proteomics, metabolomics, and transcriptomics (6-8). The most modern suggested name for these approaches is Medomics (9). Since these traditional scoring systems are based on visual and subjective interpretations of analog reading, the integration of these outputs is highly challenging (Figure 1). The emergence of the fields of quantification and integration is a unique opportunity in future prospects of medicine.

Medical interpretation of CT, MRI, and PET images is a simple visual interpretation of contrast. Although this interpretation has been shown to be very effective in the management of cancer patients based on physician observations, it remains at a qualitative and subjective level. Quantitative image features, on the other hand, are better because of their reproducibility. Radiomics contains two basic ideas that have been developed to quantify the features of these images. First, the features of tumor at tissue, cellular, or genomic level also appear in medical imaging (10). Second, the information obtained from the image can be complementary to other given sources, thus increasing the number of features and our knowledge of the tumor (2).

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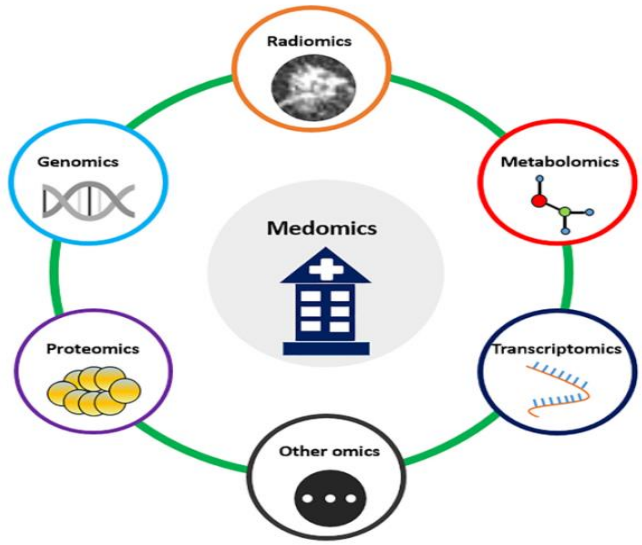

Figure 1. A range of multi-strand or multi-omics integration to form "Medomics".
Other disciplines such as pathomics and lipidomics can also be included in Medomics (9).

So far, several studies have been conducted on radiomics, its process and workflow, its features and clinical applications. Examinations based on MR, CT, and FDG PET imaging, especially for patients receiving radiotherapy, showed that many studies support the clinical signs of radiology in oncology. Most work has been done on Non-Small Cell Lung Cancer (NSCLC), head and neck, esophagus, breast, cervix and rectum. With advances in deep learning, especially with the use of Region Based Convolutional Neural Networks (R-CNN), tumor recognition has greatly expanded (11). Radiomics CT features have recently been used with the Stacking Ensemble machine learning algorithm to predict and estimate gastrointestinal radiation damage in prostate radiotherapy (12).

In a review of 553 original articles, Song et al. estimated the publication growth of radiomics articles at 177.82% in 5 years (2012-2018). Most articles were on lung, breast and prostate cancers that were monitored and described by logistic regression tools and Least Absolute Shrinkage and Selection Operator (LASSO) (13). With generally accepted standards, there are a growing number of multicenter and prospective articles that indicate an increase in the quality of future studies.

The specific purpose of this review article is to analyze the culture of radiomics image research for radiotherapy applications, to show how far image extraction research is from conventional medical applications. This study was also conducted for informing the oncology community about the use of radiomics methods in personalizing treatments, increasing effectiveness, reducing complications and costs, and showing the prospects of future medical perspectives.

Methods

This review article was approved by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.REC.1399.402 and was performed by searching the Persian and international databases PubMed, Scopus, Google Scholar, Web of Science, ISC and Magiran without time limit and using the keywords radiomics, imaging, radiotherapy and cancer.

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Most early works or early articles on the predictive features of radiomics were based on the Mann-Whitney U test, which was able to separate patients into two categories of treatment response and non-response, or the Kruskal-Wallis test, which was used for more than two types of response (14). When this feature is expressed in continuous numerical size, the feature threshold size for optimizing population classification into groups is obtained by analyzing Receiver Operating Characteristic (ROC) and calculating Area Under the Curve (AUC).

For the evaluation of prognosis and patient survival, Kaplan-Meier univariate analysis along with log-rank test followed by multivariate Cox regression are mostly used. Although most of the applications used to estimate the features were designed by the researchers themselves, here we can name some widely used applications such as: MATLAB, Pyradiomics, IBEX, Python (13).

Results

Radiomics involves the basic steps of data collection and processing, tumor segmentation, feature extraction, processing, and modeling. Since the beginning of the radiomics process, improvements have been made in each of these areas, which are discussed below. An example of an executive process or workflow of radiomics is shown in Figure 2.

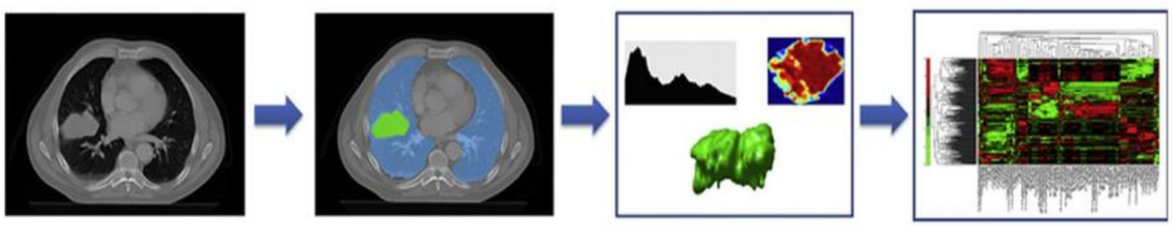

Figure 2. Radiomics workflow review

Data collection and preprocessing: radiomics always starts with data collection. Radiomics was first proposed with CT images (2) and was soon used in MRI image analysis (3). Studies have also been performed with PET images (15-17) and ultrasonography (18, 19). In the study of Song, the most frequently used imaging method was CT (43.53%) followed by MRI (35.93%) and the annual growth of MRI use compared to other imaging methods was very high (196.25%) (13). Images collected from various hospitals are reconstructed with different parameters and software. As such, these differences may have unexpected effects on the radiographic pattern (20). Studies have shown that parameters such as current and voltage of x-ray tube, slice width, voxel size, gray level, kernel convolution, and image reconstruction methods can affect the reproducibility and stability of features (21, 22). Since there is still no uniform and standard instruction for image collection, the image quality of the same tumor may vary. This affects gray surface-based features, such as histogram-based textural features. Therefore, the imaging method and the parameters involved should be strictly controlled and image preprocessing methods such as normalization and noise elimination should be performed (6). Pixel size and slice width have a huge effect on texture features and necessitate the need for post-processing sampling. Filter selection affects texture features, but the problem of contrast-enhanced images remains unresolved (23). It has recently been shown that feature calculation parameters (bin size and amplitude) may have a greater effect on the reproducibility of CT features compared to imaging parameters (effective dose, pitch, slice width and filter), which should be considered in clinical applications (24).

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Tumor segmentation: segmentation of the target area is an essential step in the radiomics process. Since very distinctive features are obtained from the segmented area, these features are used in the preparation of the template for automatic screening. The segmentation of a region of interest (ROI) can be done manually, semi-automatically or fully automatically. Of course, in the process of radiomics based on deep learning, which is another approach to extracting quantitative image parameters, segmentation is not necessary. In such approaches, image features are not predefined, but rather they are identified and generated from basic data with computational patterns. However, by performing the image segmentation here, the performance of the template is improved (4, 14).

In radiomics, almost all primary tumors are examined. Tumor segmentation determines which area must be most analyzed. Regardless of the method used, there are certain challenges. First, there is no gold standard for tumor segmentation (2). Although the manual method is often considered the gold standard, it is tedious, time consuming and user-dependent. To identify the areas of interest, the radiologist or radiation oncologist should examine individual sections of the image to form a tumor. Second, there are many structural (morphological) changes because tumors are different from geometric objects and it is difficult to model the changes. Third, the tumor margin can be blurred by the partial volume effect and not well detected in the image. In addition, the reproducibility and reliability of these structures are also very important (4).

Intraclass correlation coefficients (ICC) are used to assess interoperability. Numerous studies have shown that ROIs must be identified with an acceptable intraclass correlation coefficient, so more extracted features can be used (25, 26). On the other hand, it was shown that semi-automatic segmentation has more reproducibility and stability than manual methods (27, 28). Although segmentation methods for medical imaging have long been considered and pursued, there is still a long way ahead to have a fully automated diagnostic program.

Feature extraction:

Types of image features: Many image features have emerged in this field (29). Separate approaches based on statistics, pattern, conversion, and structure may be used to analyze the information. Features were generally separated based on the shape and size of the lesion, histogram features of the image intensity based on first-order statistics, texture features (describing the dependencies between the voxels), features based on the filter and pattern, and fractal features (figures 3 and 4).

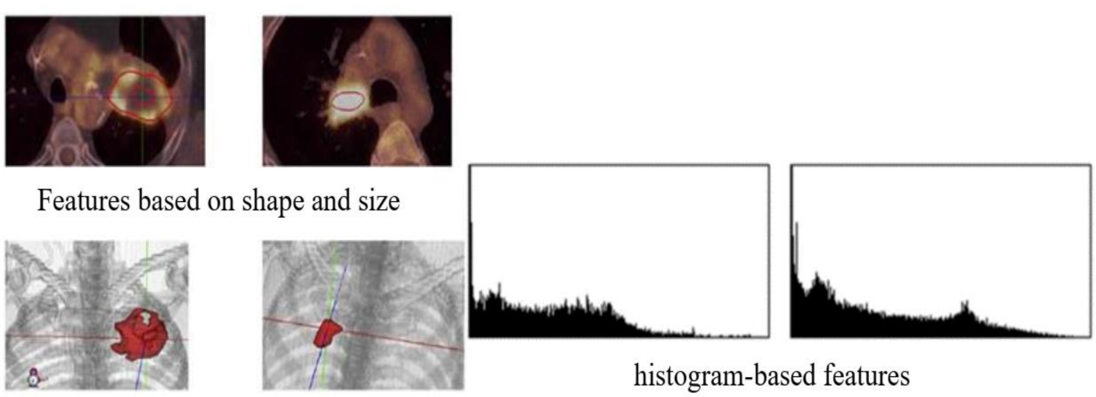

Figure 3. Features based on shape, size and histogram; schematic of two lung injuries in PET/CT imaging

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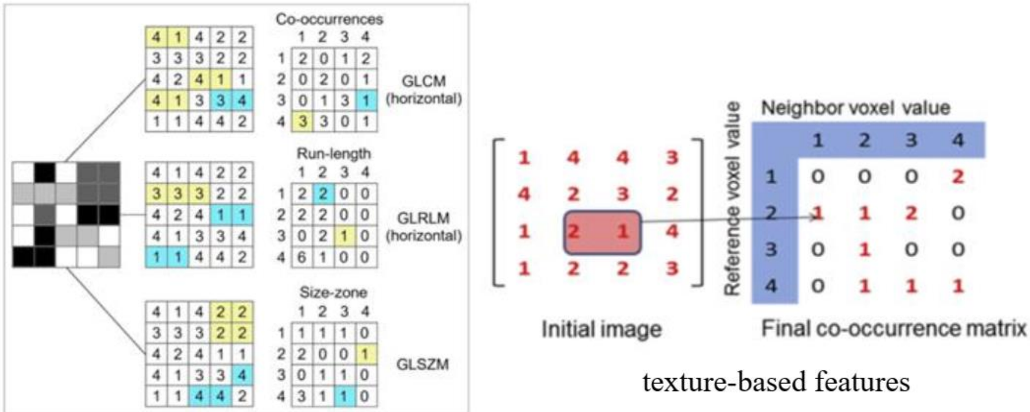

Figure 4. Examples of texture-based features (30)

Features based on shape and size: In oncology, a smaller tumor has a better prognosis than a larger tumor. Injury reduction in CT imaging is assessed by measuring the maximum injury length, which is a predictor of response to treatment (14). Tumor volume is therefore one of the first choices of quantitative imaging features. Spherical tumors with sharp edges have better outcomes than leaked tumors. Therefore, criterion-dependent imaging features of this phenomenon, such as sphericity and size, have been investigated.

Histogram-based features: In imaging, the main feature is the intensity (I) of the voxel. In CT image, this feature is represented by Hounsfield (HU) numbers, which indicate the density of tissue through which x-rays pass. This type of image is mostly used to determine the gross tumor volume (GTV) and the organ at risk (OAR).

Texture-based features: Texture analysis is a mathematical method used to describe the relationship between the intensity of pixels or voxels and their position in the image. A simple way to describe real texture is absolute gradient analysis, which reflects the degree or sudden turbulence of the image's gray surface intensity (30). For two pixels or voxels together, the gradient is highest when one is black and the other is white. If both pixels are the same color, the slope is zero there. One of the advantages of measuring texture parameters is that it is a post-processing method that can be used for standard clinical imaging data. Texture analysis in medical imaging is a promising tool designed to improve the description of abnormal images of patients to act as a predictive biomarker. However, the nature of image collection means diversity in any pixel/voxel size, which can jeopardize the usefulness of texture analysis in medicine (23).

Image Feature Selection: Feature selection methods can be divided into three categories: Filter, Wrapper, and Embedded (31). Filter (or standalone) methods evaluate features regardless of pattern. There are two main types of filter methods: univariate and multivariate methods. Univariate filters categorize most features based on quality (Chi-square or Mann-Whitney U test). Multivariate filters are set up by rankers and subset selectors, such as those used to select attribute-based features. Another widely used method of feature selection is the least absolute shrinkage and selection operator (LASSO), which can combine the selected features and a prediction pattern (32). Therefore, LASSO is a regression analysis method that performs both feature selection and adjustment based on the sum of the least squares to increase the predictive accuracy and interpretability of the constructed statistical model.

Modeling: Providing accurate and robust machine learning algorithms, deep learning, or statistical methods for categorizing or creating predictive patterns are some of the clinical applications of radiomics. However, using a large number of features of limited samples for classification and forecasting not only requires a lot of time estimation, but may not be optimal. Most current surveys are limited to a single hospital. Therefore, the conclusions suffer from lack of external evaluation or validation (4). Radiomics examinations should be routinely tested and refined with randomized, multicenter controlled clinical trials with large samples in the future. This enables radiomics to lead clinical treatments in a sharp, reliable and effective manner.

Validation: Although the growth and clinical approach of radiomics has been very high, it has always been difficult to reproduce and validate the researches in this area (12). Even for the same image, different feature sizes are produced with two implementation applications, because there are no standardized definitions of features with verifiable reference sizes, and image processing stages for feature estimation are not performed continuously. Recently, 25 research groups were able to standardize 169 of the 174 features, which in turn showed good and excellent reproducibility in the validated data set (33). The area under curve (AUC), and the sensitivity and specificity of the pattern can also be used to assess whether the pattern can predict clinical outcome. In survival analysis, consistency index and time-dependent ROC curve are mostly used for validation. In addition, calibration is a useful tool for analysis of diagnosis and survival, as it can achieve consistency between observed clinical findings and predictions of the pattern (4).

Applications of radiomics in the diagnosis and treatment of cancer: radiomics is one of the approaches and perspectives in the treatment of cancer, especially radiation therapy, which paves the way for personalization of treatment. Before treatment, this goes back to the disease stage classification and identification of genetic features. In treatment planning, one must isolate healthy and malignant tissues and better identify GTV. In the analysis of treatment outcomes, this function goes back to predicting patient survival, response to treatment, and the occurrence of distant metastases and their side effects. Using a known process such as drug production, and with some special similarities, Sollini et al. emphasized on Image Mining Discipline as the most effective way to enter a routine clinical work and prevent a new period of imaging stagnation in the upcoming decades toward a practical radiomics (34).

Lung tumors: For advanced localized adenocarcinoma of the lung, the phenotype of radiomics features of tumor was used as a prognostic biomarker that showed a strong correlation with distant metastasis (35). ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) pattern and features of CT radiomics of lung at several centers predicted local recurrence at 100% sensitivity and 96% specificity (36). In NSCLC patients, radiotherapy can affect the features of radiomics, which is known as predictor of the clinical response of the tumor at the end of radiotherapy, known as delta-radiomics (Δradiomics). Radiotherapy in combination with delta-radiomics can predict overall survival and distant metastasis (37). Radiomics studies of lung cancer focus more on the diagnosis and description of the biological features of tumor. According to the latest studies, radiomics-based patterns for lung cancer have shown the ability to determine a moderate prognosis. Future research should use standard features, select strong features, and extend pattern and deep learning methods, without the need for predefined features, to improve imaging-based patterns (38).

Head and neck tumors: The negative consequences and mortality of human papillomavirus (HPV) positive in oropharyngeal squamous cell carcinoma have been shown to be greater than its negative strain. CT imaging features can distinguish between these cancers and HPV positive and negative, and can therefore be used to select the appropriate treatment (39). Moreover, in head and neck cancers, such as oropharyngeal and non-oropharyngeal squamous cell carcinomas, different cells have different reactions and resistance to ionizing radiation. By identifying radiation-resistant cells in the tumor, special treatment methods can be suggested (40, 41). In head and neck radiotherapy, the parotid gland always receives a high dose of radiation, which in turn leads to the failure of this gland and the high prevalence of xerostomia as a common injury. Therefore, its anatomical structure and radiomics features will change after radiotherapy. The volume, mean intensity, spatial fractal, and entropy of the parotid gland decrease dramatically at various steps during radiotherapy, which can be used to monitor the response and complications of radiotherapy (42). For patients

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with glioblastoma, surgery and postoperative radiation therapy are used, and radiation therapy with uniform dose is accompanied by early recurrence. Machine learning algorithm (Support Vector Machine [SVM]) was used to measure the risk of recurrence by extracting features from the area after the operation. Therefore, based on these data and based on recurrence probability in the peritumoral region, the radiation dose intensification regimen was given (43).

Furthermore, the features of lymph node radiomics in pre-treatment CT imaging can provide useful information in predicting the response to induced chemotherapy. A radiographic pattern was constructed with LASSO regression and three features of skewness, minimum and Low Gray-Level Run Emphasis (LGRE) and a combined radiomic-clinical pattern. The combined model showed the best performance in the training and test groups. Thus, a CT-based confirmation of lymph nodes with clinical parameters showed the ability to predict nodal response to induced chemotherapy for patients with locally advanced head and neck squamous cell carcinoma (HNSCC) (44).

Prostate tumors: Much effort has been made to analyze radiomics imaging before, during, and after prostate cancer radiation therapy. Many researchers used radiographic features obtained from mp-MRI (multi-parameter MRI) before treatment to predict the biochemical recurrence of prostate cancer after radical prostatectomy, external beam radiotherapy, or brachytherapy (4). The debate over the replacement of pathological features with the findings of radiomics is still challenging. However, the development of reliable predictive patterns with machine learning typically requires hundreds of patients to perform in addition to the same number of independent datasets for pattern validation as an input for pattern making (45).

Gastrointestinal cancers: Some cancerous tumors are treated with chemotherapy or radiotherapy or mixed methods depending on the preoperative condition. After locally advanced rectal cancer (LARC) surgery, 15 to 27% of patients show a complete pathological response after neoadjuvant therapy, which means that the treatment clears the tissue from tumor cells (46, 47). Due to the high complications of surgery, TME limits the quality of life. Patients who show a complete response to neoadjuvant chemoradiotherapy will not undergo surgery. In a previous study of 411 patients with LARC who underwent neoadjuvant chemotherapy and surgery, all CT images of patients were used to calculate 271 radiomics features. Test-retest and contour-recontour results were used to filter stable radiomics and 21 effective features were recorded. Clinical findings included localized control, remote control, disease-free survival (DFS), and overall survival (OS). The findings showed that CT features could potentially predict the OS for such patients (48). In one of the most recent works on primary tumor features to predict extramural venous invasion (EMVI) in rectal cancer, radiographic nomogram with clinical features and mrEMVI showed the highest efficiency in predicting EMVI as a suitable and non-invasive tool (Figure 5). T2WI-based radiomics was also superior in predicting EMVI status in rectal cancer compared to CT and contrast-enhanced T1-weighted imaging (CE T1WI) (49). Another study of texture processing features of the initial CT image of 121 patients with LARC was given a prognostic score to lower the stage of the disease, which may lead to a more personalized treatment for each patient (50).

To predict the clinical outcome of adenocarcinoma at the site of esophageal transplantation under chemotherapy/radiotherapy, Wang et al. used the CT imaging features of 146 patients before radiotherapy (51). The findings showed that the imaging pattern could effectively classify patients into general, low-risk, moderate, and high-risk survival groups.

Validated predictive patterns for the risk of gastrointestinal stromal tumors (GISTs) may provide non-invasive and practical biomarkers to optimize treatment approaches and improve prognosis. Texture features (29 features) of CT image of 168 patients with pathological certificate of disease were extracted by LASSO regression. The combined model was superior to texture analysis alone (52). Another study showed that the

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CT features of 82 patients could differentiate between different degrees of pathology of pancreatic neuroendocrine tumors. The feature selection method of several machine learning algorithms such as distance correlation with Adaptive Boosting Classification showed a good program in this field (53). In the study of Shin et al., of 438 extracted features, a pattern of 7 features with Cox penalized regression, LASSO and ten-fold cross validation was obtained. In both internal and external validations, the size of the ROC curve (AUC) of both radiomics patterns was significantly higher than the clinical pattern. Thus, the radiomics pattern on preoperative CT images may improve RFS prediction and high-risk classification in preoperative settings of LAGC (54).

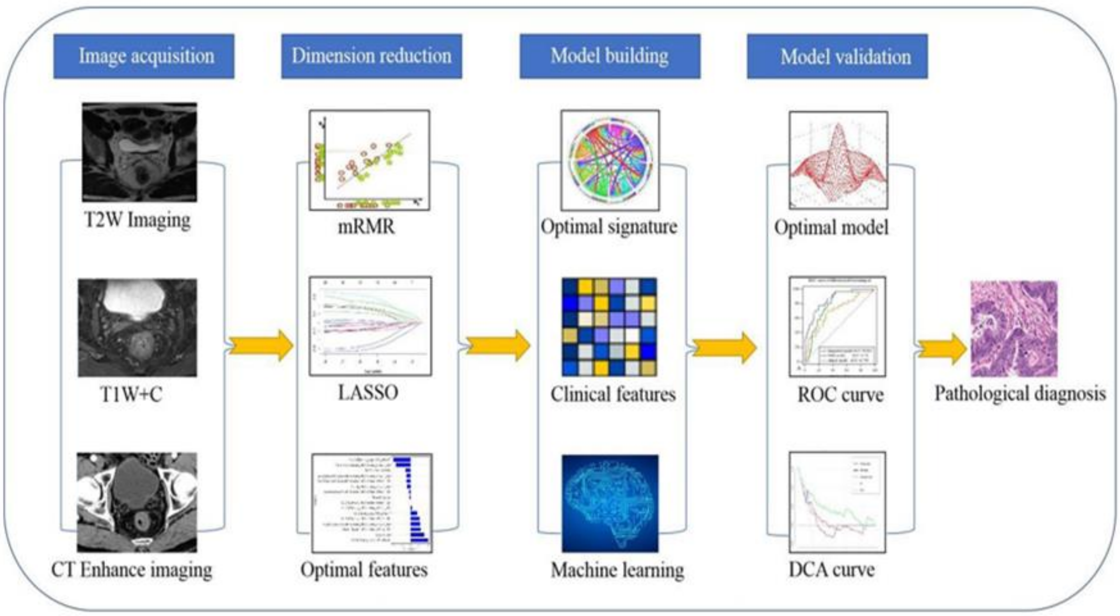

Figure 5. Radiomics pattern workflow in EMVI treatment (49)

Challenges and prospects of Radiomics: radiomics is a new and multidisciplinary field with challenges that are inevitable (3). First, there is no standard image collection method. Each of the different methods of medical imaging has advantages and disadvantages and are complementary. With such heterogeneity in diversity of image collection methods and guidelines in terms of resolution, field of view, cut width, and other metrics, it is not possible to make a proper comparison between these images (8). Second, many algorithms have been used so far to process and model this data, for which there is no specific standard. Therefore, a unified method should be established and stable and reproducible patterns should be developed to recognize radiomics as a clinical prognostic tool. Perhaps the non-reproducibility of the features is the biggest challenge to clinical interpretation or translation of radiomics (5). Third, although the sharing of medical images between centers has always been one of the major shortcomings, it has made great strides over the years with the establishment of necessary infrastructures. Therefore, standardization of radiomics algorithms is supported by having a shared database with the extracted image and features. Also, using the same data set in algorithms, it is possible to compare and validate the findings after reaching stability and sustainability. On the other hand, traditional picture archiving and communication systems (PACS) do not have the necessary ability to deploy algorithms, nor do they have the ability to integrate radiomics outputs into the clinical workflow (55). Therefore, PACS systems and current specialized radiomics tools and instruments do not have the integrated features needed to link, collaborate, and advance clinical knowledge and clinical work. In some cases, pathological assessments are not available for comparison. The novel set of imaging biomarkers proposed by radiomics should be related to serology or tissue biomarkers available through digital pathology. Optimal prediction accuracy is achieved when the training set consists of only one special imaging device (for example, Toshiba), which indicates a bias in the features of the device type or the scanning methods. This result demonstrates the importance of imaging parameters, such as hardware's parameters and instructions for teaching radiomics-based classifications. Future evaluation is based on how clinical applications of radiographic patterns and potential solutions such as feature coordination eliminate this dependence on device type (41).

Most radiomics findings have not been clinically implemented and require retrospective and prospective confirmation in clinical trials. A prerequisite for the clinical implementation of radiomics is the elimination of deficiencies. The future approaches should include a safer and more efficient pattern, the integration of multimodal imaging, such as PET-MRI and PET-CT, and the integration of multidisciplinary or multi-omics to establish "Medomics" (9).

Discussion

In this study, it was shown that with the features of these images and special software, it is possible to estimate quantitative structural information and mechanism of slice of the body. Extensive and up-to-date studies of the clinical application of radiomics in oncology support the disease stage classification, isolation of disease stages, separation between healthy and malignant tissues, showing genetic features, predicting response to treatment and predicting the type and severity of treatment side effects.

The research findings are promising but are not sufficient to be used extensively in clinical practice. By identifying radiomics as a biomarker of cancer treatment, it is hoped that important features can be extracted from the image to be used in the treatment decision-making process by processing phenotypes. Current efforts are increasingly aimed at expanding more homogeneous imaging techniques to achieve reproducible patterns. The data is also shared between centers with the aim of creating large groups of researchers to test and validate future radiomics-based hypotheses (56). Therefore, the perspective of radiomics approaches may include cancer diagnosis, markers for prognosis, determination of chemotherapeutic drugs in each individual patient, radiation dose administration, quality control of dose, healthy tissue toxicity in adaptive radiotherapy, and differentiating between radiation damage and tumor recurrence.

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