Ultrasound-based radiomics: current status, challenges and future opportunities

Yingying Jia¹,²*, Jun Yang³*, Yangyang Zhu¹, Hao Wu¹, Ying Duan¹, Kundi Chen¹, Fang Nie¹
* the authors share the first authorship

¹Ultrasound Medicine Center, Lanzhou University Second Hospital, Lanzhou, Gansu, ²Department of Ultrasound, People’s Hospital of Ningxia Hui Nationality Autonomous Region, Yinchuan, Ningxia, ³Department of Urology, People’s Hospital of Ningxia Hui Nationality Autonomous Region, Yinchuan, Ningxia, China.

Abstract

Ultrasound (US) imaging is part of conventional medical imaging in clinical practice that is low-cost, non-ionizing, portable and capable of real-time image acquisition and display. However, in certain cases, US has limited sensitivity and specificity in differentiating between malignant and benign lesions. Ultrasound-based radiomics, as a new branch of radiomics, can provide additional features such as heterogeneity of lesions that are invisible to the naked eye, alone or in combination with demographic, histological, genomic or proteomic data, thereby improving the accuracy of US in diagnosis of disease. This article provides an introduction to ultrasound-based radiomics, covering its workflow, the application of machine learning, and current research status. Current limitations of radiomics, such as consistency of image acquisition, parameter variations, and difficulty in calibrating quantitative methods in ultrasound, will also be covered.

Keywords: radiomics; ultrasound; artificial intelligence; machine learning

Introduction

Radiomics is a relatively new discipline involving high-throughput extraction of image features from medical images [1-3]. They are combined with genetic and clinical data, using artificial intelligence methods to extract tumor features based on pathophysiology, molecular biology and other related information, providing clinical practices to assist treatment decision-making [4,5]. At present, radiomics plays a necessary role in the auxiliary diagnosis of disease, prediction of tumor biological behavior, and evaluation of treatment response. There have been several radiomics studies on computed tomography (CT), magnetic resonance imaging (MRI) and pathology [6-9]. As an important branch of medical imaging, ultrasound (US) is a real-time, dynamic and convenient imaging practice that does not cause radiation damage and involves wide coverage and multiple imaging modes [10]. US-based radiomics is a rapidly evolving technology with significant challenges and opportunities. So far, there have been studies in various fields, such as thyroid [11], breast [12], liver [13], obstetrics [14], prostate [15] and rectum [8]. With continuous updates in the image processing technology and the application of machine learning (ML) algorithms, US-based radiomics has broad application prospects. Radiomics features are not only correlated with genomic data but also may provide complementary information regarding tumor heterogeneity across the entire tumor to improve survival prediction and risk stratification. In the era of personalized medicine, US-based radiomics has the potential to improve diagnostic ability, predict prognosis and assess treatment responses.

The workflow of US-based radiomics (fig 1)

Image and data acquisition

US images used for radiomics analysis should be standardized and be of a high quality. The Digital Im-
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aging and Communications in Medicine format is often the preferred format for medical images. There are several modalities for US imaging, including B-mode, color Doppler, contrast-enhanced ultrasound (CEUS) and elastography. The more modalities involved, the more radiomics features can be extracted.

Meanwhile, clinical data and laboratory indicators related to the disease should be collected. Several studies have reported higher diagnostic efficiency of the clinical-radiomics model than that of the single radiomics model [16]. As for the estimation of data size, according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines [17], the sample size of the training set in the clinical prediction model is calculated according to events per variable (EPV); that is, the number of positive events corresponding to each independent variable, which is recommended to meet EPV=10 at least.

**Region of interest (ROI) segmentation**

The methods for delineating an ROI include automatic, semi-automatic, or manual methods. The ROI in the image is delineated to segment the image [18]. Manual delineation remains a common method employed to improve the accuracy of tumor boundary delineation. ROI delineation by different people or at different time points can reduce differences in manual delineation [19]. The ROIs delineated can be masses, tumor subregions, metastases, carcinomas with paracancerous tissues, and even normal tissues. Braman et al found that radiomics analysis of carcinomas and paracancerous tissue can successfully predict a complete response to neoadjuvant chemotherapy in breast cancer [20].

**Feature extraction and selection**

Radiomics features are extracted from the training sets and verified in the independent validation sets. The extracted features mainly include shape features, first-order gray histogram features, second-order and higher-order texture features, and other features based on filtering and transformation [21]. Some researchers believe that high-order features and second-order texture features can reflect internal tumor heterogeneity to a certain extent, which provides helpful information for improving the diagnostic efficiency of tumors and predicting a treatment response [22]. Because radiomics features are highly correlated, the analysis of high-dimensional features may cause problems in multicollinearity and overfitting [23]. The Lasso regression method can reduce data dimension and help in selecting the optimal features.

**Task-oriented modeling: establishment, evaluation, and validation**

Evaluation of the clinical prediction model mainly includes the discrimination, calibration, and value of the clinical application. Discrimination can be reported in terms of the receiver operating characteristic (ROC) curve or the area under the ROC curve (AUC) [24]. Calibration refers to the consistency between the observed results and model prediction. The most common method to display this is to draw a calibration curve. The closer the curve is to the diagonal, the better the calibration of the model. A good prediction model should have a high degree of discrimination and calibration, but these two indicators are not completely isolated.

Common validation methods include random split validation, cross-validation, bootstrap method, and “in-
ternal-external” cross-validation. External validation evaluates the performance of the model for new data by using data that have not been used in model establishment, including time and spatial validation. External validation is more reliable than internal validation, which improves the repeatability of the study [25,26].

**Machine learning, deep learning and transfer learning in US-based radiomics**

*Traditional ML*

ML is part of artificial intelligence that aims to construct algorithms that can learn from and make predictions on data [27]. ML includes supervised, semi-supervised and unsupervised learning (fig 2). Supervised ML [28] refers to labeling radiomics features using classification and regression methods, learning from labeled features and providing labels to unlabeled new data. Semi-supervised learning refers to the classification, regression and clustering methods employed to label the training set’s radiomics features, whereas the validation set is not labeled [29]. Unsupervised learning classifies radiomics features using clustering methods of data compression, dimension reduction, and feature filtering [30]. The input data of unsupervised learning are raw and unlabeled, so the computer cannot know its exact type. It can only rely on the powerful computation ability to analyze data characteristics and to classify the data based on similar characteristics. Based on the classification results, the significance of different classification representatives is analyzed. Common algorithms in ML include K-nearest neighbor, decision tree, random forest, support vector machine (SVM), logistic regression, linear discriminant analysis, multilayer perceptron and bayes model [31]. In order to establish the model with the best diagnostic performance, it is necessary to build the model using several ML methods and select the best one. Fleury et al [32] studied the discrimination of five ML models for benign and malignant breast tumors and found that the SVM classifier model had a better diagnostic performance, with ROC-AUC reaching 0.84.

*Deep learning (DL)*

DL is a method in the field of ML that extracts non-linear features from the data. Neural networks are built from numerous perceptual layers using convolutional neural networks to directly extract features, thereby automatically learning relevant model features and data characteristics from a large-scale dataset for a specific problem to accomplish classification and prediction. A review comprehensively summarized the research on DL in medical image classification, detection and segmentation and registration and retrieval [33]. There are many DL methods, among which neural network learning [34] is the most commonly used one in ultrasound-based radiomics. In recent years, DL has increasingly been applied in ultrasound-based radiomics [35], reducing the uncertainty of manual input. Furthermore, it greatly compensates for the poor robustness of ultrasonic images and plays a crucial role in the development of ultrasound-based radiomics. DL requires higher input data than traditional ML.

*Transfer learning (TL)*

TL is an ML method that has great potential in ultrasound-based radiomics analysis. By fine-tuning the model on a new dataset, knowledge obtained from one dataset can be easily transferred to a new dataset, which is obtained from another center using another ultrasound device [36] (fig 3). Thus, it avoids the overfitting problem caused by insufficient training data in conventional DL. In case of insufficient sample size, TL has excellent advantages; with gradual accumulation of sample size, new samples, as the external validation set of the model, can continuously improve the performance of the model. A study on liver fibrosis classification based on US showed that TL was significantly more effective than non-TL in diagnosis [37].

**Clinical application of US-based radiomics**

In clinical practice, US is widely used to detect morphological abnormalities in organs (Table I). With the development of US-based radiomics, more imaging bio-
Table I. List of typical papers of Ultrasound-based radiomics

| Organ of body location | Modality | Number of patients | Multi-center Yes or No | Prospective Yes or No | Modeling approach | Application | Reference |
|------------------------|----------|--------------------|------------------------|-----------------------|-------------------|-------------|-----------|
| Breast                 | Gray-scale | 206              | N                      | N                     | ML                | Classification (benign and malignant nodes) | [32]       |
|                        | Gray-scale | 196              | N                      | N                     | Logistic regression | Predicting presurgical ALN metastasis status in Breast cancer | [68]       |
| Liver                  | Gray-scale and SWE | 466              | N                      | N                     | TL                | Liver fibrosis grading | [37]       |
|                        | Gray-scale,CEUS | 196              | N                      | Y                     | ML                | Predicting presurgical ALN metastasis status in Breast cancer | [55]       |
|                        |            | 144              | N                      | Y                     | ML                | Liver fibrosis grading | [15]       |
| SWE                    | Gray-scale | 398              | Y                      | Y                     | DL                | Liver fibrosis grading | [57]       |
|                        | Gray-scale | 2143             | Y                      | Y                     | DL                | Classification of malignant from benign FLLs | [47]       |
|                        | Gray-scale | 482              | N                      | N                     | Logistic regression | Prediction of microvascular invasion in hepatocellular carcinoma | [74]       |
|                        | Gray-scale | 668              | N                      | N                     | Logistic regression | Predicting Different Histopathological Subtypes of Primary Liver Cancer. | [13]       |
| CEUS                   |           | 419              | N                      | N                     | DL                | Prediction of PFS and treatment selection of HCC patients | [82]       |
| CEUS / TIC / Gray scale|           | 130              | N                      | N                     | DL                | Predicting personalized responses of HCC to TACE | [83]       |
| Thyroid                | Gray-scale | 1734             | N                      | N                     | DL / TL           | Classification (benign and malignant nodes) | [39]       |
|                        | Gray-scale | 2064             | N                      | N                     | ML                | Classification (benign and malignant nodes) | [11]       |
|                        | Gray-scale | 1894             | Y                      | Y                     | TL                | Lymph node metastasis prediction of papillary thyroid carcinoma | [64]       |
|                        | Gray-scale | 96               | N                      | N                     | ML                | Predicting BRAF Mutation in Papillary Thyroid Carcinoma | [70]       |
| Ovary                  | Gray-scale | 348              | N                      | N                     | ML                | Classification (benign and malignant ovarian tumors) | [50]       |
| Fetal lung             | Gray-scale | 548              | N                      | Y                     | ML                | Analyze the fetal lung texture at different situation | [90]       |
| Rectal                 | Gray-scale and SWE | 127              | N                      | Y                     | DL                | Prediction of tumor deposits in rectal cancer | [80]       |
markers will appear through deeper image extraction that cannot be seen under the naked eye, enabling earlier and more accurate non-invasive diagnosis of diseases.

**Benign and malignant differentiation**

The most common use of US-based radiomics assisted diagnosis is the differentiation between benign and malignant tumors. Due to the superficial position of the thyroid and the high quality of US images, US-based radiomics was first applied to distinguish between benign and malignant thyroid nodules [38-41]. Zhang et al [11] extracted the radiomics features from 2064 pathologically confirmed B-mode and elastography images of thyroid nodules and established a diagnostic model using the random forest algorithm. This model’s ability to differentiate between benign and malignant thyroid nodules was better than that of experienced imaging physicians. Similarly, there are several studies on US-based radiomics for diagnosing benign and malignant breast masses, some of which only extracted radiomics features from B-mode US images, while others combined B-mode and elastography images [42,43]. US features of triple-negative breast cancer are not typical. Lee et al [44] successfully differentiated triple-negative breast cancer from breast fibroadenoma using texture analysis. The Breast Imaging Reporting and Data System (BI-RADS) is a standard method for evaluating breast nodules. However, significant intra-observer and inter-observer differences based on the BI-RADS have been reported [45]. Luo et al [46] studied 315 cases of high-risk breast lesions with category 4 or 5 and established a prediction model based on radiomics combined with the BI-RADS classification. The model showed a high degree of differentiation between benign and malignant (AUC 0.928; 95% CI [0.876, 0.908]). B-mode US has a limited ability in the diagnosis of focal hepatic diseases. In a multicenter study [47], US-based radiomics analysis of 2143 focal liver lesions showed that the radiomics model had high accuracy and specificity in differentiating between benign and malignant liver lesions, and the diagnostic ability was superior to that of radiologists with a work experience of 15 years and the diagnostic accuracy was comparable to that of contrast-enhanced CT. Peng et al [13] used US-based radiomics to distinguish among different pathological subtypes of primary liver cancer preoperatively, which helps in accurate clinical diagnosis and treatment. Similarly, Qin et al [48] developed radiomics models of B-mode US signatures for determining the origin of primary tumors in metastatic liver disease, with satisfactory AUC values reflected in the training and testing sets. Prostate HistoScanning (PHS) is a computer-based (ML classifier) system trained to identify changes suggestive of PCa in unprocessed 3D-reconstructed ultrasound radiofrequency data. A recent study reported that patients with suspected PCa could benefit from additional PHS targeting guided biopsies [49]. Besides, US-based radiomics has also been applied in the differential diagnosis of benign and malignant ovarian tumors [50], true and pseudo gallbladder polyps [51] and endometrial cancer [52].

**Diffuse lesion of the liver**

Accurate assessment of liver fibrosis grading is crucial for treatment decision-making and prognosis prediction [53]. So far, liver biopsy has remained the gold standard for liver fibrosis classification. However, a biopsy is invasive and its results are affected by sampling errors; additionally, it may cause bleeding, infection and other serious complications. Therefore, several studies have employed US-based radiomics for liver fibrosis classification. Different US modalities and ML algorithms have been used to predict liver fibrosis classification, and all have a good diagnostic accuracy [37,54-56]. A multicenter prospective study [57] using DL on radiomics of shear wave elastography (SWE) of the liver reported significantly improved diagnostic efficiency for evaluating liver fibrosis in chronic hepatitis B, with the ability to diagnose F4 and ≥F3 liver fibrosis approaching pathological levels. Liu et al [58] used convolutional neural network to analyze radiomics features of the liver capsule and then used SMV to distinguish patients with liver fibrosis; the AUC reached 0.92. Tang et al [59] developed an ML model based on quantitative US parameters using SWE in rats and reported a significantly improved classification accuracy of steatohepatitis.

**Evaluation of tumor biological behaviors and molecular profiles**

Cancer progression is accompanied by complex physiological and biochemical changes in the tumor and its surrounding environment. Morphological features of primary lesions have a certain relationship with tumor biological behavior, such as lymph node metastasis, invasion, pathological grade and differentiation [60]. However, some of these microscopic morphological features are invisible to the naked eye. Imaging biomarkers are expected to be extracted through radiomics analysis and the biological behavior of these lesions can be preoperatively evaluated non-invasively.

Lymph node metastasis is an essential basis for tumor node metastasis (TNM) staging. Preoperative determination of lymph node metastasis is of great importance in selecting treatment methods and in patients’ prognosis [61]. A meta-analysis showed that US, CT and MRI could not accurately evaluate lymph node metastasis because the current imaging methods mainly used lymph node size as the sole criterion for metastasis. Radiomics,
on the other hand, provides a solution to this problem [62]. Chen et al [63] retrospectively analyzed the radiomics features of 115 patients with rectal cancer and established a multiparametric prediction model with high discrimination and calibration in predicting lymph node metastasis in rectal cancer using US, elastography and CT images of primary lesions, paracancerous tissues and maximal lymph nodes. Similarly, several studies have conducted radiomics analyses on multimodal US for papillary thyroid carcinoma (PTC) and reported significantly improved accuracy of prediction of cervical lymph node metastasis in PTC [64-66]. Jin et al [67] developed a non-invasive radiomics method based on the textural features from US images to detect lymph node metastasis in patients with early-stage cervical cancer. Different ML methods have also been used to build different models, such as the radiomics and clinical-radiomics model, for predicting axillary lymph node metastasis in early-stage breast cancer [12,68,69].

Several studies have demonstrated a strong relationship between imaging features and the underlying tumor genetics, which may provide a biological basis for the clinical applications of radiomics [3]. Recently, Kwon et al [70] performed a radiomics analysis on sonograms from 96 cases of PTC confirmed by pathology; 86 radiomics features were obtained and a prediction model was established, which showed moderate performance and predicted BRAF mutations in PTC. However, in another study [71], radiomics features extracted from 527 US images showed limited value as a non-invasive biomarker for predicting the presence of BRAFV600E mutation of PTC regardless of size.

Radiogenomics features provide valuable biomarkers. There are several quantitative analyses of US images that reflect tumor biology at the cellular and molecular level. Guo et al [72] demonstrated that US-based radiomics features extracted from breast cancer imaging can discriminate tumors with different estrogen and progesterone receptor expression (AUC=87.7%). Microvascular invasion (MVI) [73], which is defined as the invasion of tumor cells within a vascular space lined by the endothelium, has been widely demonstrated as a predictor of the early recurrence of hepatocellular carcinoma (HCC). Hu et al [74] extracted radiomics features from gray-scale US images of 482 patients with HCC and established a clinical-radiomics prediction model combining AFP and tumor size, which showed an excellent predictive value for MVI positivity.

Similarly, Yao et al [75] performed a radiomics analysis on multimodal US images of 177 patients with focal liver lesions, extracted 2046 radiomics features and established five ML models, which exhibited good diagnostic and predicted performance for the differentiation of benign and malignant and the level of biomarkers such as PD-1, Ki-67 and MVI. Cholangiocarcinoma (ICC) is an aggressive primary hepatic carcinoma originating in the bile duct epithelium [76]. Unlike HCC, surgical resection is currently the only treatment method for patients with ICC [77]. A study [78] extracted the most predictive radiomics features for evaluating MVI, perineural invasion, differentiation, Ki-67, VEGFR and CK7 in ICC and reported that these features had moderate efficiency in non-invasively predicting the biological behavior of ICC.

Tumor deposits (TDs) in rectal cancer are defined as focal clusters of adenocarcinoma that are located in the pericolic or perirectal fat near the primary tumor and not associated with the primary tumor or lymph nodes [79]. TDs are related to the TNM stage. TD positive means that the tumor is more aggressive and has a worse prognosis. It is difficult to make a definite diagnosis of TD positive by conventional imaging and can only be determined by postoperative pathology. Chen et al [80] analyzed the gray-scale and elastography US image features of 127 patients with rectal cancer and realized the preoperative prediction of TD-positive.

**Treatment decision-making and prognosis evaluation**

Surgical resection (SR) and radiofrequency ablation (RFA) are the two main treatment strategies for the diagnosis of early HCC [81]. Nevertheless, the choice of treatment for the individual remains controversial. Liu et al [82] optimized the treatment of early HCC based on the DL of radiomics in CEUS, which not only predicted the progression-free survival (PFS) of RFA and SR patients but also identified that 17.3% of RFA patients and 27.3% of SR patients should be required to exchange treatment options, which could increase the 2-year PFS by 12% and 15%, respectively. Liu et al [83] developed and validated a DL model of radiomics based on CEUS (R-DLCEUS), a ML model based on the radiomics of CEUS time-intensity curve (R-TIC) and a ML based on the radiomics of gray-scale images (R-B mode) to predict the treatment response of patients with HCC after personalized transhepatic arterial chemoembolization. The R-DLCEUS reported the highest diagnostic efficacy of 0.93 (95% CI, 0.80-0.98) and could effectively achieve accurate and personalized prediction. Similarly, Ma et al [84] developed a combined model based on preoperative dynamic CEUS image, conventional US and clinical factors of HCC lesions to predict early and late recurrence in patients with a single HCC lesion ≤5 cm in diameter after thermal ablation, which showed a good performance (training cohort: AUC 0.89, test cohort: AUC 0.84). Park
et al [85] evaluated and predicted the disease-free survival of PTC based on the radiomics features of B-mode US, which is expected to provide personalized diagnosis and treatment and reduce the overtreatment of thyroid cancer. Current US-based radiomics studies are mostly based on images from a single time point, whereas with regard to tumor response to treatment, the effectiveness of treatment can be predicted through a comparative analysis of images from multiple time points during treatment. A multi-center study showed that US-based radiomics could monitor treatment response to neoadjuvant chemotherapy in patients with locally advanced breast cancer [86].

**Shortcomings and future opportunities**

According to the radiomics quality score [87], high-quality imaging, more standardized data collection and processing, more information from new US imaging technology, multi-center joint and external validation set, more time points, prospective study based on the molecular biology and pathology bases can improve the quality of radiomics studies [19].

The relatively unfixed US sections, operator dependence and inconsistency of device and parameter settings are the major reasons why the development of US-based radiomics is failing to keep up with the development of other medical imaging methods. Additionally, US features can only be extracted from a single section of the lesion, so it cannot reflect the whole tumor, which is also a limitation of the application of US-based radiomics. At present, the number of images in most radiomics studies based on US imaging is in the hundreds, while the number of thousands of cases is still within a small number.

Moreover, most of the studies are single-center studies, which limits the generalization of ML models. Most studies based on US-based radiomics are retrospective. Prospective design can improve the quality of the study but needs more workload and time. Another challenge is the weak interpretability between currently extracted radiomics features and clinical features.

With the improvement of the image processing technology, development of artificial intelligence methods suitable for US-based radiomics and continuous improvement of device resolution, US-based radiomics have increased prospects. DL has been proven to significantly improve performance over traditional ML methods [88], while avoiding complex pre-processing. TL is also an effective method for classifying the relatively small databases that are currently available. TL has been proposed to be more applicable in US-based radiomics analysis. The shortcomings of US imaging can be compensated by continuously increasing the number of images and external validation to improve the diagnostic efficiency of the model. Besides, to achieve better image consistency, unified image acquisition standards [2,89,90], device parameters and ROI outline sites are needed [19]. Also, the development of radiomics based on multimodal DL models (B-mode, Doppler, CEUS, and shear wave elastography) provides complementary information that can improve the diagnostic efficiency of the model [36]. With the breakthrough of dynamic video processing technology, the CEUS dynamic video or three-dimensional ultrasound can provide more spatial-temporal data and extract more valuable radiomics features, which is another breakthrough in the field of ultrasound-based radiomics studies.

**Conclusion**

Here, we reviewed the current status of US-based radiomics, covering its workflow, the application of ML and the clinical application of US-based radiomics together with limitations and future opportunities. Many researchers have proposed to use radiomic features from medical images to quantify various tumor phenotypes, describe the heterogeneity and utilize these features as predictors of genetics and clinical outcomes. Despite the promising clinical potential of radiomics, precautions must be taken in designing high-quality radiomics studies. The usefulness of radiomic features as well as their potential in predicting clinical data strongly depends on an acquisition method and processing and segmentation strategies. Standardized image acquisition protocols, multi-modalities US imaging, adequate size, completeness of prospective datasets, advanced image analysis, processing technology, and suitable ML algorithms for US-based radiomics will stimulate new vitality in the application of ultrasound diagnosis.

**Conflict of interest:** none

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