Review

Med Ultrason 2022, Vol. 24, no. 4, 451-460
DOI: 10.11152/mu-3248

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

Yingying Jia[1,2*], Jun Yang[3*], Yangyang Zhu[1], Hao Wu[1], Ying Duan[1], Kundi Chen[1], Fang Nie[1]

** the authors share the first authorship*

[1]Ultrasound Medicine Center, Lanzhou University Second Hospital, Lanzhou, Gansu, [2]Department of Ultrasound, People's Hospital of Ningxia Hui Nationality Autonomous Region, Yinchuan, Ningxia, [3]Department 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.

Received 08.05.2021 Accepted 30.09.2021
Med Ultrason
2022, Vol. 24, No 4, 451-460
Corresponding author: Fang Nie
Department of Ultrasound, Lanzhou University Second Hospital, Chengguan District, Lanzhou, Gansu, 730000
Phone: 13993163088 (China)
E-mail: ery_nief@lzu.edu.cn

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-

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-

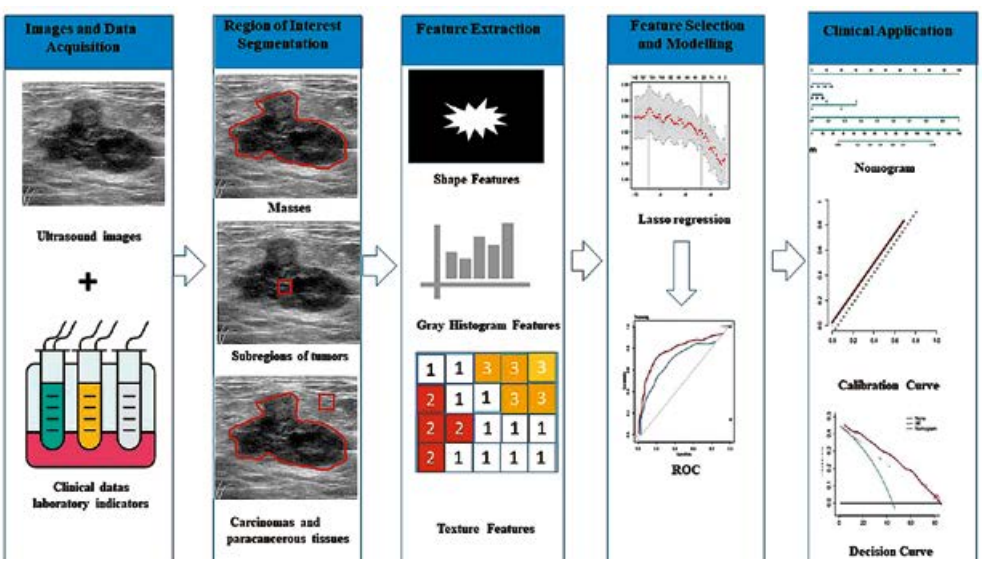


Fig 1. Work-flow of ultrasound-based radiomics

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 nonlinear 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

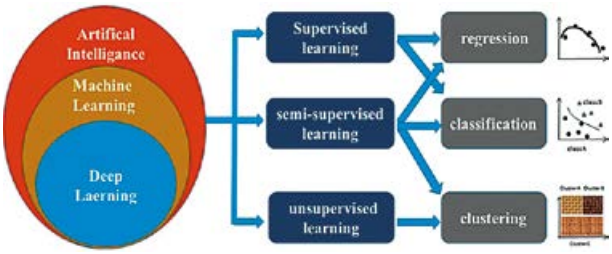


Fig 2. Artificial intelligence, including machine learning and deep learning and their tasks.

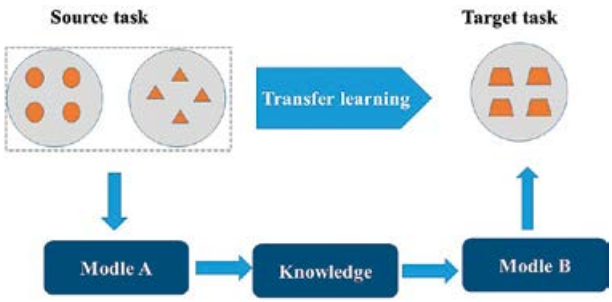


Fig 3. Learning process of Transfer learning

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-scal,CEUS	196 144	N N	Y Y	ML ML	Predicting presurgical ALN metastasis status in Breast cancer Liver fibrosis grading	[55]
	SWE	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 hepato-cellular 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-sacle	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 situa-tion	[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

References

1. Bai HX, Lee AM, Yang L, et al. Imaging genomics in cancer research: limitations and promises. Br J Radiol 2016;89:20151030.
2. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology 2016;278:563-577.
3. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 2012;48:441-446.
4. Aerts HJ, Velazquez ER, Leijenaar RT, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 2014;5:4006.

5. Sun R, Orlhac F, Robert C, et al. In Regard to Mattonen et al. Int J Radiat Oncol Biol Phys 2016;95:1544-1545.
6. Song J, Shi J, Dong D, et al. A New Approach to Predict Progression-free Survival in Stage IV EGFR-mutant NSCLC Patients with EGFR-TKI Therapy. Clin Cancer Res 2018;24:3583-3592.
7. Sun C, Tian X, Liu Z, et al. Radiomic analysis for pretreatment prediction of response to neoadjuvant chemotherapy in locally advanced cervical cancer: A multicentre study. EBioMedicine 2019;46:160-169.
8. Cui Y, Yang X, Shi Z, et al. Radiomics analysis of multiparametric MRI for prediction of pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer. Eur Radiol 2019;29:1211-1220.
9. Zeng C, Nan Y, Xu F, et al. Identification of glomerular lesions and intrinsic glomerular cell types in kidney diseases via deep learning. J Pathol 2020;252:53-64.
10. Brattain LJ, Telfer BA, Dhyani M, Grajo JR, Samir AE. Machine learning for medical ultrasound: status, methods, and future opportunities. Abdom Radiol (NY) 2018;43:786-799.
11. Zhang B, Tian J, Pei S, et al. Machine Learning-Assisted System for Thyroid Nodule Diagnosis. Thyroid 2019;29:858-867.
12. Yu FH, Wang JX, Ye XH, Deng J, Hang J, Yang B. Ultrasound-based radiomics nomogram: A potential biomarker to predict axillary lymph node metastasis in early-stage invasive breast cancer. Eur J Radiol 2019;119:108658.
13. Peng Y, Lin P, Wu L, et al. Ultrasound-Based Radiomics Analysis for Preoperatively Predicting Different Histopathological Subtypes of Primary Liver Cancer. Front Oncol 2020;10:1646.
14. Ghorayeb SR, Bracero LA, Blitz MJ, Rahman Z, Lesser ML. Quantitative Ultrasound Texture Analysis for Differentiating Preterm From Term Fetal Lungs. J Ultrasound Med 2017;36:1437-1443.
15. Wildeboer RR, Schalk SG, Demi L, Wijkstra H, Mischi M. Three-dimensional histopathological reconstruction as a reliable ground truth for prostate cancer studies. Biomed Phys Eng Express 2017;3:035014.
16. Dong D, Tang L, Li ZY, et al. Development and validation of an individualized nomogram to identify occult peritoneal metastasis in patients with advanced gastric cancer. Ann Oncol 2019;30:431-438.
17. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1-W73.
18. Polan DF, Brady SL, Kaufman RA. Tissue segmentation of computed tomography images using a Random Forest algorithm: a feasibility study. Phys Med Biol 2016;61:6553-6569.
19. Ma X, Wei J, Gu D, et al. Preoperative radiomics nomogram for microvascular invasion prediction in hepatocellular carcinoma using contrast-enhanced CT. Eur Radiol 2019;29:3595-3605.
20. Braman NM, Etesami M, Prasanna P, et al. Intratumoral and peritumoral radiomics for the pretreatment prediction of pathological complete response to neoadjuvant chemotherapy based on breast DCE-MRI. Breast Cancer Res 2017;19:57.
21. Wei M, Du Y, Wu X, et al. A Benign and Malignant Breast Tumor Classification Method via Efficiently Combining Texture and Morphological Features on Ultrasound Images. Comput Math Methods Med 2020;2020:5894010.
22. Lubner MG, Smith AD, Sandrasegaran K, Sahani DV, Pickhardt PJ. CT Texture Analysis: Definitions, Applications, Biologic Correlates, and Challenges. Radiographics 2017;37:1483-1503.
23. Berenguer R, Pastor-Juan MDR, Canales-Vázquez J, et al. Radiomics of CT Features May Be Nonreproducible and Redundant: Influence of CT Acquisition Parameters. Radiology 2018;288:407-415.
24. Obuchowski NA, Bullen JA. Receiver operating characteristic (ROC) curves: review of methods with applications in diagnostic medicine. Phys Med Biol 2018;63:07TR01.
25. Zhao B, James LP, Moskowitz CS, et al. Evaluating variability in tumor measurements from same-day repeat CT scans of patients with non-small cell lung cancer. Radiology 2009;252:263-272.
26. Zhao B, Tan Y, Tsai WY, et al. Reproducibility of radiomics for deciphering tumor phenotype with imaging. Sci Rep 2016;6:23428.
27. Lo YC, Rensi SE, Torng W, Altman RB. Machine learning in chemoinformatics and drug discovery. Drug Discov Today 2018;23:1538-1546.
28. Jiang T, Gradus JL, Rosellini AJ. Supervised Machine Learning: A Brief Primer. Behav Ther 2020;51:675-687.
29. Li YF, Guo LZ, Zhou ZH. Towards Safe Weakly Supervised Learning. IEEE Trans Pattern Anal Mach Intell 2021;43:334-346.
30. Lin K, Lu J, Chen CS, Zhou J, Sun MT. Unsupervised Deep Learning of Compact Binary Descriptors. IEEE Trans Pattern Anal Mach Intell 2019;41:1501-1514.
31. Deo RC. Machine Learning in Medicine. Circulation 2015;132:1920-1930.
32. Fleury E, Marcomini K. Performance of machine learning software to classify breast lesions using BI-RADS radiomic features on ultrasound images. Eur Radiol Exp 2019;3:34.
33. Litjens G, Kooi T, Bejnordi BE, et al. A survey on deep learning in medical image analysis. Med Image Anal 2017;42:60-88.
34. Shin HC, Roth HR, Gao M, et al. Deep Convolutional Neural Networks for Computer-Aided Detection: CNN Architectures, Dataset Characteristics and Transfer Learning. IEEE Trans Med Imaging 2016;35:1285-1298.
35. Sahiner B, Pezeshk A, Hadjiiski LM, et al. Deep learning in medical imaging and radiation therapy. Med Phys 2019;46:e1-e36.
36. Akkus Z, Cai J, Boonrod A, et al. A Survey of Deep-Learning Applications in Ultrasound: Artificial Intelligence-Powered Ultrasound for Improving Clinical Workflow. J Am Coll Radiol 2019;16:1318-1328.

37. Xue LY, Jiang ZY, Fu TT, et al. Transfer learning radiomics based on multimodal ultrasound imaging for staging liver fibrosis. Eur Radiol 2020;30:2973-2983.
38. Liang J, Huang X, Hu H, et al. Predicting Malignancy in Thyroid Nodules: Radiomics Score Versus 2017 American College of Radiology Thyroid Imaging, Reporting and Data System. Thyroid 2018;28:1024-1033.
39. Zhou H, Jin Y, Dai L, et al. Differential Diagnosis of Benign and Malignant Thyroid Nodules Using Deep Learning Radiomics of Thyroid Ultrasound Images. Eur J Radiol 2020;127:108992.
40. Bhatia KS, Lam AC, Pang SW, Wang D, Ahuja AT. Feasibility Study of Texture Analysis Using Ultrasound Shear Wave Elastography to Predict Malignancy in Thyroid Nodules. Ultrasound Med Biol 2016;42:1671-1680.
41. Park VY, Lee E, Lee HS, et al. Combining radiomics with ultrasound-based risk stratification systems for thyroid nodules: an approach for improving performance. Eur Radiol 2021;31:2405-2413.
42. Zhang Q, Xiao Y, Suo J, et al. Sonoelastomics for Breast Tumor Classification: A Radiomics Approach with Clustering-Based Feature Selection on Sonoelastography. Ultrasound Med Biol 2017;43:1058-1069.
43. Youk JH, Kwak JY, Lee E, Son EJ, Kim JA. Grayscale Ultrasound Radiomic Features and Shear-Wave Elastography Radiomic Features in Benign and Malignant Breast Masses. Ultraschall Med 202041:390-396.
44. Lee SE, Han K, Kwak JY, Lee E, Kim EK. Radiomics of US texture features in differential diagnosis between triple-negative breast cancer and fibroadenoma. Sci Rep 2018;8:13546.
45. Schwab F, Redling K, Siebert M, et al. Inter- and Intra-Observer Agreement in Ultrasound BI-RADS Classification and Real-Time Elastography Tsukuba Score Assessment of Breast Lesions. Ultrasound Med Biol 2016;42:2622-2629.
46. Luo WQ, Huang QX, Huang XW, Hu HT, Zeng FQ, Wang W. Predicting Breast Cancer in Breast Imaging Reporting and Data System (BI-RADS) Ultrasound Category 4 or 5 Lesions: A Nomogram Combining Radiomics and BI-RADS. Sci Rep 2019;9:11921.
47. Yang Q, Wei J, Hao X, et al. Improving B-mode ultrasound diagnostic performance for focal liver lesions using deep learning: A multicentre study. EBioMedicine 2020;56:102777.
48. Qin H, Wu YQ, Lin P, et al. Ultrasound Image-Based Radiomics: An Innovative Method to Identify Primary Tumorous Sources of Liver Metastases. J Ultrasound Med 2021;40:1229-1244.
49. 49. Glybochko PV, Alyaev YG, Amosov AV, et al. Evaluation of Prostate HistoScanning as a Method for Targeted Biopsy in Routine Practice. Eur Urol Focus 2019;5:179-185.
50. Martinez-Mas J, Bueno-Crespo A, Khazendar S, et al. Evaluation of machine learning methods with Fourier Transform features for classifying ovarian tumors based on ultrasound images. PLoS One 2019;14:e0219388.
51. Yuan HX, Yu QH, Zhang YQ, Yu Q, Zhang Q, Wang WP. Ultrasound Radiomics Effective for Preoperative Identification of True and Pseudo Gallbladder Polyps Based on Spatial and Morphological Features. Front Oncol 2020;10:1719.
52. Michail G, Karahaliou A, Skiadopoulos S, et al. Texture analysis of perimenopausal and post-menopausal endometrial tissue in grayscale transvaginal ultrasonography. Br J Radiol 2007;80:609-616.
53. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
54. D'Souza JC, Sultan LR, Hunt SJ, et al. B-mode ultrasound for the assessment of hepatic fibrosis: a quantitative multiparametric analysis for a radiomics approach. Sci Rep 2019;9:8708.
55. Li W, Huang Y, Zhuang BW, et al. Multiparametric ultrasomics of significant liver fibrosis: A machine learning-based analysis. Eur Radiol 2019;29:1496-1506.
56. Wang J, Guo L, Shi X, Pan W, Bai Y, Ai H. Real-time elastography with a novel quantitative technology for assessment of liver fibrosis in chronic hepatitis B. Eur J Radiol 2012;81:e31-e36.
57. Wang K, Lu X, Zhou H, et al. Deep learning Radiomics of shear wave elastography significantly improved diagnostic performance for assessing liver fibrosis in chronic hepatitis B: a prospective multicentre study. Gut 2019;68:729-741.
58. Liu X, Song JL, Wang SH, Zhao JW, Chen YQ. Learning to Diagnose Cirrhosis with Liver Capsule Guided Ultrasound Image Classification. Sensors (Basel) 2017;17:149.
59. Tang A, Destrempes F, Kazemirad S, Garcia-Duitama J, Nguyen BN, Cloutier G. Quantitative ultrasound and machine learning for assessment of steatohepatitis in a rat model. Eur Radiol 2019;29:2175-2184.
60. Takahashi D, Kojima M, Morisue R, et al. Comparison of morphological features in lymph node metastasis between pancreatic neuroendocrine neoplasms and pancreatic ductal adenocarcinomas. Pancreatology 2020;20:936-943.
61. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471-1474.
62. Li XT, Sun YS, Tang L, Cao K, Zhang XY. Evaluating local lymph node metastasis with magnetic resonance imaging, endoluminal ultrasound and computed tomography in rectal cancer: a meta-analysis. Colorectal Dis 2015;17:O129-O135.
63. Chen LD, Liang JY, Wu H, et al. Multiparametric radiomics improve prediction of lymph node metastasis of rectal cancer compared with conventional radiomics. Life Sci 2018;208:55-63.
64. Yu J, Deng Y, Liu T, et al. Lymph node metastasis prediction of papillary thyroid carcinoma based on transfer learning radiomics. Nat Commun 2020;11:4807.
65. Zhou SC, Liu TT, Zhou J, et al. An Ultrasound Radiomics Nomogram for Preoperative Prediction of Central Neck Lymph Node Metastasis in Papillary Thyroid Carcinoma. Front Oncol 2020;10:1591.

66. Liu T, Ge X, Yu J, et al. Comparison of the application of B-mode and strain elastography ultrasound in the estimation of lymph node metastasis of papillary thyroid carcinoma based on a radiomics approach. Int J Comput Assist Radiol Surg 2018;13:1617-1627.
67. Jin X, Ai Y, Zhang J, et al. Noninvasive prediction of lymph node status for patients with early-stage cervical cancer based on radiomics features from ultrasound images. Eur Radiol 2020;30:4117-4124.
68. Qiu X, Jiang Y, Zhao Q, Yan C, Huang M, Jiang T. Could Ultrasound-Based Radiomics Noninvasively Predict Axillary Lymph Node Metastasis in Breast Cancer? J Ultrasound Med 2020;39:1897-1905.
69. Zheng X, Yao Z, Huang Y, et al. Deep learning radiomics can predict axillary lymph node status in early-stage breast cancer. Nat Commun 2020;11:1236.
70. Kwon MR, Shin JH, Park H, Cho H, Hahn SY, Park KW. Radiomics Study of Thyroid Ultrasound for Predicting BRAF Mutation in Papillary Thyroid Carcinoma: Preliminary Results. AJNR Am J Neuroradiol 2020;41:700-705.
71. Yoon JH, Han K, Lee E, et al. Radiomics in predicting mutation status for thyroid cancer: A preliminary study using radiomics features for predicting BRAFV600E mutations in papillary thyroid carcinoma. PLoS One 2020;15:e0228968.
72. Guo Y, Hu Y, Qiao M, et al. Radiomics Analysis on Ultrasound for Prediction of Biologic Behavior in Breast Invasive Ductal Carcinoma. Clin Breast Cancer 2018;18:e335-e344.
73. Lim KC, Chow PK, Allen JC, et al. Microvascular invasion is a better predictor of tumor recurrence and overall survival following surgical resection for hepatocellular carcinoma compared to the Milan criteria. Ann Surg 2011;254:108-113.
74. Hu HT, Wang Z, Huang XW, et al. Ultrasound-based radiomics score: a potential biomarker for the prediction of microvascular invasion in hepatocellular carcinoma. Eur Radiol 2019;29:2890-2901.
75. Yao Z, Dong Y, Wu G, et al. Preoperative diagnosis and prediction of hepatocellular carcinoma: Radiomics analysis based on multi-modal ultrasound images. BMC Cancer 2018;18:1089.
76. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int 2019;39 Suppl 1:19-31.
77. Tang Y, Wang L, Teng F, Zhang T, Zhao Y, Chen Z. The clinical characteristics and prognostic factors of combined Hepatocellular Carcinoma and Cholangiocarcinoma, Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma after Surgical Resection: A propensity score matching analysis. Int J Med Sci 2021;18:187-198.
78. Peng YT, Zhou CY, Lin P, et al. Preoperative Ultrasound Radiomics Signatures for Noninvasive Evaluation of Biological Characteristics of Intrahepatic Cholangiocarcinoma. Acad Radiol 2020;27:785-797.
79. Greene FL. Tumor deposits in colorectal cancer: a moving target. Ann Surg 2012;255:214-215.
80. Chen LD, Li W, Xian MF, et al. Preoperative prediction of tumour deposits in rectal cancer by an artificial neural network-based US radiomics model. Eur Radiol 2020;30:1969-1979.
81. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
82. Liu F, Liu D, Wang K, et al. Deep Learning Radiomics Based on Contrast-Enhanced Ultrasound Might Optimize Curative Treatments for Very-Early or Early-Stage Hepatocellular Carcinoma Patients. Liver Cancer 2020;9:397-413.
83. Liu D, Liu F, Xie X, et al. Accurate prediction of responses to transarterial chemoembolization for patients with hepatocellular carcinoma by using artificial intelligence in contrast-enhanced ultrasound. Eur Radiol 2020;30:2365-2376.
84. Ma QP, He XL, Li K, et al. Dynamic Contrast-Enhanced Ultrasound Radiomics for Hepatocellular Carcinoma Recurrence Prediction After Thermal Ablation. Mol Imaging Biol 2021;23:572-585.
85. Park VY, Han K, Lee E, et al. Association Between Radiomics Signature and Disease-Free Survival in Conventional Papillary Thyroid Carcinoma. Sci Rep 2019;9:4501.
86. Quiaoit K, DiCenzo D, Fatima K, et al. Quantitative ultrasound radiomics for therapy response monitoring in patients with locally advanced breast cancer: Multi-institutional study results. PLoS One 2020;15:e0236182.
87. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol 2017;14:749-762.
88. Brehar R, Mitrea DA, Vancea F, et al. Comparison of Deep-Learning and Conventional Machine-Learning Methods for the Automatic Recognition of the Hepatocellular Carcinoma Areas from Ultrasound Images. Sensors (Basel) 2020;20:3085.
89. Yip SS, Aerts HJ. Applications and limitations of radiomics. Phys Med Biol 2016;61:R150-R166.
90. Du Y, Fang Z, Jiao BDJ, et al. Application of ultrasound-based radiomics technology in fetal lung texture analysis in pregnancies complicated by gestational diabetes or preeclampsia. Ultrasound Obstet Gynecol 2021;57:804-812.