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CANCER INNOVATION

REVIEW

Progress in research on ultrasound radiomics for predicting the prognosis of breast cancer

Xuantong Gong[1] | **Xuefeng Liu**[2] | **Xiaozheng Xie**[3] | **Yong Wang**[1]

[1]Department of Ultrasound, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2]State Key Laboratory of Virtual Reality Technology and Systems, School of Computer Science and Engineering, Beijing Advanced Innovation Center for Big Data and Brain Computing (BDBC), Beihang University, Beijing, China

[3]School of Computer and Communication Engineering, University of Science and Technology Beijing, Beijing, China

Correspondence
Yong Wang, Department of Ultrasound, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China.
Email: drwangyong77@163.com

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Abstract

Breast cancer is the most common malignant tumor and the leading cause of cancer-related deaths in women worldwide. Effective means of predicting the prognosis of breast cancer are very helpful in guiding treatment and improving patients' survival. Features extracted by radiomics reflect the genetic and molecular characteristics of a tumor and are related to its biological behavior and the patient's prognosis. Thus, radiomics provides a new approach to noninvasive assessment of breast cancer prognosis. Ultrasound is one of the commonest clinical means of examining breast cancer. In recent years, some results of research into ultrasound radiomics for diagnosing breast cancer, predicting lymph node status, treatment response, recurrence and survival times, and other aspects, have been published. In this article, we review the current research status and technical challenges of ultrasound radiomics for predicting breast cancer prognosis. We aim to provide a reference for radiomics researchers, promote the development of ultrasound radiomics, and advance its clinical application.

KEYWORDS
breast cancer, deep learning, prognosis prediction, radiomics, ultrasound

1 | BACKGROUND

According to the 2020 global cancer statistics released by the International Agency for Research on Cancer, female breast cancer has the highest incidence worldwide and its mortality ranks fifth among cancers, posing a serious threat to women's life and health [1]. Although doctors have aimed to improve the 5-year survival rate of patients with breast cancer by adopting comprehensive treatment plans that include surgery, radiotherapy, chemotherapy,

Abbreviations: ALN, axillary lymph node; AUC, area under the curve; CEUS, contrast-enhanced ultrasound; CUS, conventional ultrasound; DFS, disease-free survival; NAC, neoadjuvant chemotherapy; SWE, shear wave elastography; TNM, tumor node metastasis.

targeted therapy, and immunotherapy, the prognosis is still poor once recurrence and metastases occur [2]. It is very important to develop an effective means of predicting the prognosis of breast cancer because this would have far-reaching significance in guiding treatment and improving patients' survival.

The features extracted by radiomics reflect the genetic and molecular characteristics of a tumor and are related to its biological behavior and the patient's prognosis [3–5]. With the development of computer-aided technology, radiomics is being used more frequently as a noninvasive means of predicting breast cancer prognosis [6–8]. Radiomics includes engineered features (traditional machine learning methods), which extract quantitative information from images in a high-throughput manner, and deep learning, a process that simulates analysis by the human brain by building neural networks [9]. Both of these features can be associated with the prognosis of breast cancer and used to build a clinical prediction model. Ultrasound is commonly used to screen for breast cancer and for follow-up, because it is inexpensive, involves no irradiation, and is reproducible. Ultrasound radiomics uses traditional machine learning and deep learning methods to transform ultrasound images into mineable quantitative data and construct models for supporting diagnosis and assessing prognosis. However, the clinical application of ultrasound radiomics is limited by the dependence of ultrasound image quality on humans. At present, to the best of our knowledge, there are no published reviews or summaries of the research status and technical challenges of ultrasound radiomics for predicting the prognosis of breast cancer. In this article, we aimed to summarize and analyze the value of using ultrasound radiomics to predict the prognosis of breast cancer from four perspectives: conventional ultrasound (CUS) radiomics, radiomics of new ultrasound technology, existing technology challenges, and future prospects.

2 | CONVENTIONAL ULTRASOUND (CUS) RADIOMICS

CUS is the most common means of ultrasonic diagnosis of breast cancer, and the acquisition of images is relatively simple. Radiomics can extract information that doctors cannot identify from images of primary breast cancer. It can then associate that information with lymph node status, molecular subtypes of breast cancer, treatment response, tumor recurrence, survival time, and other patient characteristics, thus providing evidence-based support for making decisions in the clinic [10–15]. The workflow of ultrasound radiomics generally includes image acquisition, image segmentation, model construction and validation, and database establishment [16].

Currently, CUS radiomics is mostly used to assist preoperative, noninvasive diagnosis of molecular subtypes of breast cancer. Research has mainly focused on the diagnosis of triple-negative, luminal type, and human epidermal growth factor receptor-2 positive breast cancer with an area under the curve (AUC) range of approximately 0.76–0.93 [17–21]. In addition, Jiang et al. [22] have constructed a deep convolutional neural network based on 4828 CUS images from 1275 patients for diagnosing the four molecular subtypes of breast cancer. The accuracy of this model is reportedly 80.07% (95% confidence interval [CI]: 76.49–83.23) to 97.02% (95% CI: 95.22–98.16) and 87.94% (95% CI: 85.08–90.31) to 98.83% (95% CI: 97.60–99.43) for the two test cohorts of each subtype. Furthermore, Zhang et al. [21] combined CUS with mammography images from 3360 paired cases and proposed multimodal deep learning with intra- and intermodality attention modules to predict molecular subtypes of breast cancer. The accuracy of the model was 88.5% (95% CI: 86.0–90.9). The purpose of these models is to avoid unnecessary biopsies and to guide preoperative treatment.

Studies have shown that CUS radiomics can accurately evaluate the efficacy of neoadjuvant chemotherapy (NAC) for breast cancer and contribute to decisions on the extent of surgery and modification of treatment plans [23–25]. Jiang et al. [23] constructed a deep learning radiomics model for preoperatively predicting the pathological complete response of locally advanced breast cancer. This model is based on pre- and post-NAC ultrasound images and has an AUC of 0.94 (95% CI: 0.91–0.97) for independent external validation. It also outperformed radiologists (AUC of radiomic signature [RS] 1 = 0.82, 95% CI: 0.76–0.87; AUC of RS2 = 0.92, 95% CI: 0.90–0.96). This outperformance occurs because the changes that occur in a tumor and its microenvironment when that tumor responds to treatment are not easy for humans to identify on ultrasound images. However, radiomics can capture these subtle changes and is, therefore, a more sensitive means of evaluating response to treatment [26, 27]. Gu et al. [24] developed a deep learning radiomics model for predicting the response to NAC in breast cancer at an early stage with AUCs of 0.812 (95% CI: 0.770–0.851) and 0.937 (95% CI: 0.913–0.955) for evaluating efficacy after the second and fourth courses of NAC, respectively. In addition, the researchers explored the interpretability of the model and found that it primarily focused on changes within the tumor after the second course of NAC and changes in the surrounding tissues after the fourth course of NAC; this increases the clinical applicability of the model.

CUS radiomics can also be used to evaluate the disease-free survival (DFS) of breast cancer patients after surgery [8, 28, 29]. Previous studies have shown a correlation between ultrasound findings and prognostic factors for breast cancer. On this basis, radiomics can obtain richer information and predict prognosis more accurately [30–32]. Xiong et al. [8] established a radiomics nomogram for predicting DFS in invasive breast cancer with a C-index of 0.796 (95% CI: 0.70–0.89) and found that CUS radiomics features are potential imaging biomarkers for risk stratification of DFS in patients with invasive breast cancer. In addition, Yu et al. [28] developed a radiomics nomogram based on intratumoral and peritumoral ultrasound features for estimating the DFS in triple-negative breast cancer with an external validated C-index of 0.71 (95% CI: 0.66–0.76). This model was more effective than the clinicopathological model and tumor node metastasis (TNM) staging system ($p < 0.01$).

3 | CONTRAST-ENHANCED ULTRASOUND (CEUS) AND ELASTOGRAPHY RADIOMICS

CEUS continuously and dynamically reflects the microcirculatory perfusion of tumors. CEUS radiomics can extract richer information from CEUS images and videos; this information has been shown to be beneficial in improving the accuracy of diagnosis of breast cancer [33, 34]. Besides, CEUS radiomics features can be used to evaluate the histological features of breast cancer with high specificity (84.62%–88.24%) [35]. However, there is a lack of relevant research on the application of CEUS radiomics in predicting the duration of survival, recurrence, and metastasis of breast cancer. Previous studies have shown that the qualitative and quantitative characteristics of CEUS are related to the prognosis of breast cancer [36, 37]. Therefore, the value of the clinical application of CEUS radiomics in predicting the prognosis of breast cancer needs further investigation.

Elastography is an ultrasonic technology that reflects the stiffness of tissues, shear wave elastography (SWE) being the most widely used index. In breast cancer, greater stiffness of a lesion according to SWE is associated with predictors of a poor prognosis [38, 39]. Traditional SWE has a limited ability to predict axillary lymph node (ALN) metastasis, with reported AUCs being only 0.585–0.719 [40]. Zheng et al. [41] used deep learning methods to deep mine the image features of SWE and achieved excellent prediction performance (AUC = 0.902, 95% CI: 0.843–0.961). Thus, a model based on SWE images can also accurately evaluate the tumor burden in the ALNs (AUC = 0.905, 95% CI: 0.814–0.996). In addition, Jiang et al. [10] have developed and validated an ultrasound elastography radiomics nomogram for preoperative evaluation of the ALN burden in patients with early stage breast cancer. This nomogram discriminated between disease-free axillary (N0) and any axillary metastases (N+ (≥1)) and achieved a C-index of 0.817 (95% CI: 0.769–0.865) for the validation cohort. Further, the nomogram discriminated between low (N+ (1–2)) and heavy metastatic ALN burden (N+ (≥3)) and achieved a C-index of 0.810 (95% CI: 0.755–0.864) for the validation cohort. Elastography combined with CUS radiomics improves the performance of the prediction model and can better assist doctors in individualizing treatment.

4 | TECHNICAL CHALLENGES

Although radiomics has many applications in diagnosing breast cancer and predicting its prognosis, there is overwhelming evidence that the prediction model studies have been of poor quality [42, 43]. Thus, applying radiomics to diagnosis and treatment is still a considerable challenge.

First, there is a lack of uniform standards for operating procedures. Since the quality of ultrasonic image acquisition is highly dependent on the operator, whether the predicted results of radiomics depend on the model and parameters of the ultrasonic machine needs to be further investigated by large studies. Thus far, radiomics studies of ultrasonic imaging are less available and more difficult to interpret than radiomics studies of other imaging methods such as magnetic resonance imaging and mammography. To help researchers perform high-quality and reproducible studies, in 2017, Lambin et al. [44] proposed an evaluation of the quality of radiomics research through a radiomics quality score, the aim being to facilitate the standardization of radiomics research. A simplified version of this score is shown in Table 1.

In addition, traditional radiomics research requires human involvement, which increases the uncertainty of the results. Some researchers have attempted to improve ways of addressing this problem [45, 46]. For example, Lee et al. [45] standardized the values of radiomics features. There is currently no generally accepted effective method; however, deep learning can learn features of images independently and output relevant results, improving the reproducibility of the method. As yet, deep learning models still cannot be interpreted reliably. More supportive clinical evidence and further research are still needed.

TABLE 1 Simplified radiomics quality score (cited from Lambin et al. [44]): 36 points denote 100% quality.

	Criteria	Points
1	Image protocol quality—well-documented image protocols (e.g., contrast, slice thickness, energy, etc.) and/or usage of public image protocols	+ 1 (if protocols are well-documented) + 1 (if the public protocol is used)
2	Multiple segmentations (segmentation by different physicians/algorithms/software, perturbing segmentations by noise, segmentation at different breathing cycles)	+1
3	Phantom study on all scanners—detect interscanner differences and vendor-dependent features	+1
4	Imaging at multiple time points—collect images of individuals at additional time points	+1
5	Feature reduction or adjustment for multiple testing: overfitting is inevitable if the number of features exceeds the number of samples. Consider feature robustness when selecting features	+3 (if either measure is implemented) −3 (if neither measure is implemented)
6	Multivariable analysis with non-radiomics features	+1
7	Detect and discuss biological correlates	+1
8	Cut-off analyses—determine risk groups by either the median, a previously published cut-off, or report a continuous risk variable	+1
9	Discrimination statistics—report discrimination statistics and their statistical significance. One can also apply the resampling method	+ 1 (discrimination statistic and its statistical significance are reported) +1 (if a resampling method technique is also applied)
10	Calibration statistics—report calibration statistics and their statistical significance. One can also apply the resampling method	+1 (if a discrimination statistic and its statistical significance are reported) + 1 (if a resampling method technique is applied)
11	Prospective study registered in a trial database	+7
12	Validation—the validation is performed without retraining and without adaptation of the cut-off value, provides crucial information concerning credible clinical performance	−5 (unverified) +2 (validation from the same institute) + 3 (another institute) + 4 (two distinct institutes) + 5 (three or more datasets from distinct institutes)
13	Comparison to the gold standard	+2
14	Report on current and potential clinical utility	+2
15	Cost-effectiveness analysis	+1
16	Open science and data—make code and data publicly available	+1 (scans open) + 1 (ROI segmentation open) + 1 (code open) + 1 (radiomics features are calculated on a set of representative ROIs and the calculated features and representative ROIs are open)

Abbreviation: ROI, region of interest.

5 | FUTURE PROSPECTS

Currently, the TNM staging system remains the primary basis for clinical evaluation of the prognosis of breast cancer. The development of radiomics provides doctors with a noninvasive means of comprehensively evaluating the heterogeneity of breast cancer. CUS radiomics has great potential in predicting the prognosis of breast cancer patients. Thus, the development of a multimodal prediction model that combines ultrasonic techniques such as CEUS and elastography is a potential direction for future research.

Furthermore, most radiomics studies have been small and retrospective. Although they can theoretically predict the prognosis of breast cancer, they are still at a clinical research stage [47]. In the future, large, multicenter, high-quality studies are needed to enable the clinical application of the results of radiomics

research and to promote the development of precision treatment strategies for breast cancer.

6 | CONCLUSIONS

Ultrasound radiomics is a noninvasive, relatively mature means of comprehensively evaluating tumor heterogeneity and diagnosing breast cancer. However, the evaluation of breast cancer patients' responses to therapy and prognosis is still at a preliminary research stage. A future promising research direction is the development of multimodal prediction models that combine patients' clinical data, pathological results, gene expression, multiple images, and other data. Notably, high-quality radiomics studies are needed to advance the clinical application of radiomics in the accurate diagnosis and treatment of breast cancer.

AUTHOR CONTRIBUTIONS

Xuantong Gong: Conceptualization (supporting); writing—review and editing (lead). **Xuefeng Liu**: Writing—review and editing (supporting). **Xiaozheng Xie**: Investigation (equal). **Yong Wang**: Conceptualization (lead); writing—review and editing (supporting).

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

ORCID

Xuantong Gong http://orcid.org/0000-0001-8984-5461

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