DOI: https://doi.org/10.53555/nnmhs.v9i5.1666 Publication URL: https://nnpub.org/index.php/MHS/article/view/1666

EXPLORING BREAST CANCER RESPONSE PREDICTION TO NEOADJUVANT SYSTEMIC THERAPY USING MRI-BASED RADIOMICS: A SYSTEMATIC REVIEW

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Abstract

Breast cancer affects more than one out of every ten persons diagnosed with cancer each year, making it the most common type of cancer in women. It is the second most common cause of cancer-related death among females worldwide. The milk-producing glands are placed in front of the chest wall, according to breast anatomy. Breast cancer progression is almost often missed. The majority of people find out they have the illness through a normal test. Others may present with an unintentional breast lump, a change in the shape or size of their breasts, or a discharge from their nips. When compared to adjuvant chemotherapy, NST allows for in vivo tumor response, tumor size reduction (allowing for breast-conserving therapy where mastectomy was recommended), and pathologic complete response (pCR). Breast cancer tumor response to NST can be predicted using imaging modalities. Breast magnetic resonance imaging (MRI) is the most effective imaging modality for evaluating tumors and predicting response. Its precision in evaluating and forecasting tumor response to NST is insufficient to change clinical treatment. NST tumor response cannot be predicted using pretreatment MRI. As a result, breast MRI accuracy must be continuously enhanced. Despite large methodological heterogeneity in each step of the radiomics workflow, studies focusing on MRI-based radiomics for tumor response prediction to NST in breast cancer patients yielded promising results.

Katakunci: *Breast cancer; MRI-based radiomics; Neoadjuvant; Systemic therapy*

PENDAHULUAN

More than one out of every ten people who are diagnosed with cancer every year has breast cancer, making it the most frequent type of cancer found in females. It is the second most common form of cancer-related death that occurs in females all over the world. According to the breast's anatomy, the glands that produce milk are located in front of the chest wall.[1] They are supported by the pectoralis major muscle, and there are ligaments that bind the breast to the chest wall and lie underneath the breasts themselves. The breast is made up of anywhere from fifteen to twenty lobes that are grouped in a circular pattern.[2,3]

The size and shape of the breasts are determined by the layer of fat that covers the lobes. The glands that are responsible for milk production in response to hormone stimulation are contained within lobules that constitute each lobe. Lobes are formed by lobules.[4] The progression of breast cancer is almost often undetected. The majority of people learn that they have the condition during the course of their routine screening. Others can present with a breast lump that was found by accident, a change in the form or size of their breasts, or a discharge from their nips.[5]

On the other hand, mastalgia is not an uncommon condition. The diagnosis of breast cancer requires a series of tests, including a physical exam, imaging (particularly mammography), and a tissue sample. Early detection results in a higher chance of surviving the disease. The tumor has a propensity to spread through the lymphatic and hematological systems, which ultimately results in distant metastasis and a bad prognosis. This explains why breast cancer screening programs are so important and stresses their significance.[5–7] Breast cancer treatment is increasingly using neoadjuvant systemic therapy (NST).[8]

NST allows in vivo tumor response, tumor size reduction (allowing breast-conserving therapy where mastectomy was suggested), and pathologic complete response (pCR) compared to adjuvant chemotherapy. Imaging modalities can predict breast cancer tumor response to NST.[4,8,9] Breast magnetic resonance imaging (MRI) is the best imaging modality for tumor evaluation and response prediction. Its accuracy in measuring and predicting tumor response to NST is insufficient to alter clinical treatment. Pretreatment MRI cannot predict NST tumor response. Thus, breast MRI accuracy must be improved continuously.[10]

This article proved the breast cancer response prediction to neoadjuvant systemic therapy using MRI-based radiomics.

METHODS

Protocol

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist was used as the basis for the establishment of the criteria that govern the methodology of this particular systematic review.

Eligibility Criteria

This systematic review was developed to analyze papers on breast cancer response prediction to neoadjuvant systemic therapy using MRI-based radiomics. These are the subjects that were mentioned in the evaluated studies. In order for you're the study to be evaluated, the following requirements must be met: 1) Articles must be fully accessible online; 2) Articles must be written in English; and 3) Articles must have been published between 2018 and the time of this systematic review's preparation. Text submissions of the following kind will not be accepted under any circumstances: 1) Letters to the editor, 2) contributions without a Digital Object Identifier (DOI), and 3) article reviews and comparable submissions.

Search Strategy

The search for studies to be included in the systematic review was carried out from May 1st, 2023 using the PubMed and SagePub databases by inputting the words: "breast cancer"; "response"; "neoadjuvant systemic therapy" and "MRI-based radiomics". Where *("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND response[All Fields] AND ("neoadjuvant therapy"[MeSH Terms] OR ("neoadjuvant"[All Fields] AND "therapy"[All Fields]) OR "neoadjuvant therapy"[All Fields] OR ("neoadjuvant"[All Fields] AND "systemic"[All Fields] AND "therapy"[All Fields]) OR "neoadjuvant systemic therapy"[All Fields]) AND MRI-based[All Fields] AND radiomics[All Fields])* is used as search keywords.

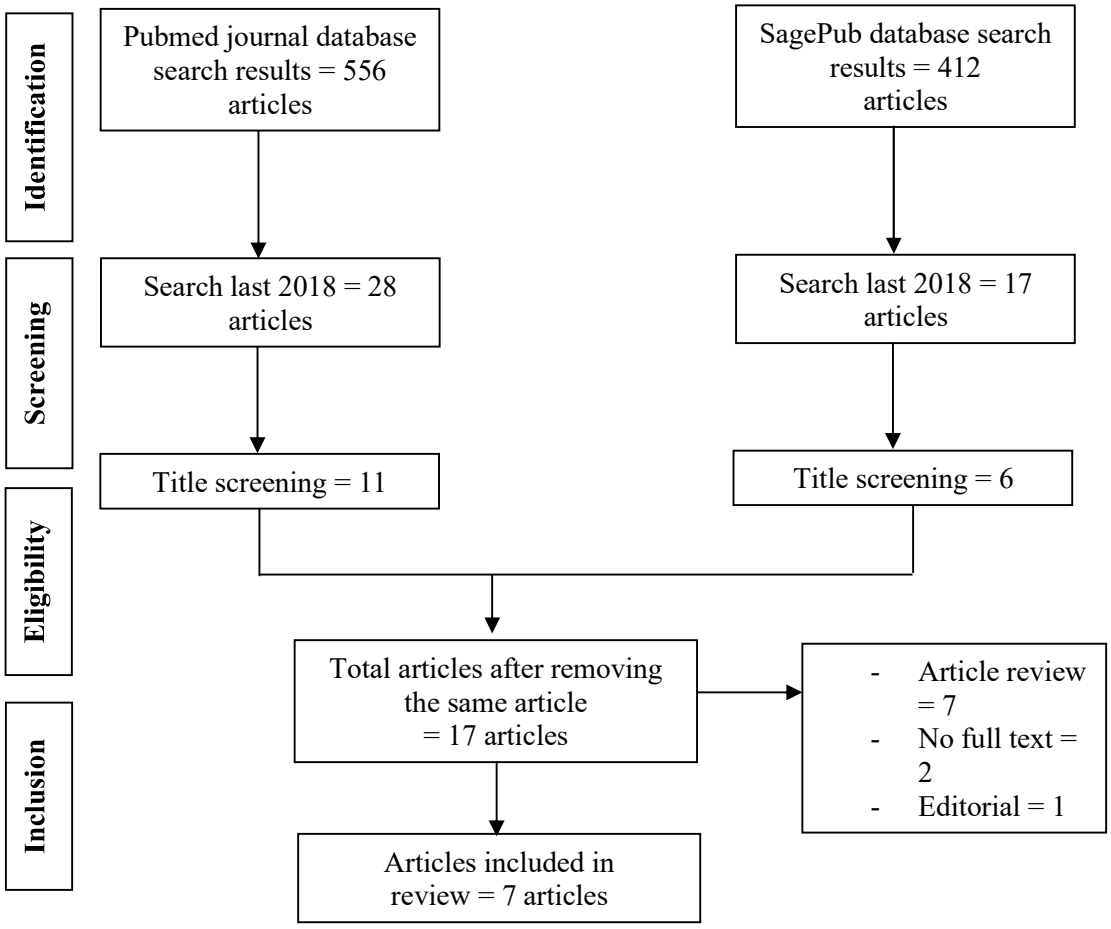

Figure 1. Article search flowchart

Data retrieval

After conducting a literature search and reading the titles and abstracts of previously published studies, the study's author changed the criteria for what should and should not be included in the study. During the compilation of the systematic review, only those research projects that were successful in meeting all of the conditions were considered. Each unique study can be identified by its title, author, publication date, origin of study location, research study design, and research variables. This information is presented in a specific format for your review and consideration.

Quality Assessment and Data Synthesis

The authors did their own independent reviews of a selection of studies discovered in the titles and abstracts of the papers to identify which studies would be qualified for consideration. The full texts of the studies that qualify for inclusion in the systematic review will then be evaluated to identify which papers can be used as final inclusions for the purposes of the review.

RESULT

Study by Bitencourt (2020)[11] showed the final model used three MRI characteristics (two clinical, one radiomic) to predict HER2 heterogeneity, with a sensitivity of 99.3% (277/279), specificity of 81.3% (26/32), and diagnostic accuracy of 97.4% (303/311). The final model for predicting predict pathologic response (pCR) included six MRI parameters (two clinical, four radiomic) with a sensitivity of 86.5% (32/37), specificity of 80.0% (20/25), and diagnostic accuracy of 83.9% (52/62) (test set); these results were independent of age and ER status, and outperformed the best model developed using only clinical parameters (p = 0.029, proportion Chi-squared test).

Leithner, et al (2020)[12] conducted a study with 91 patents. The following classification accuracies were obtained for lesions segmented on DWI and propagated to ADC maps: luminal B vs. HER2-enriched, 94.7% (based on COM features); luminal B vs. others, 92.3% (COM, HIS); and HER2-enriched vs. others, 90.1% (RLM, COM). For lesions segmented directly on ADC maps, improved results were obtained with the following classification accuracies: luminal B versus HER2-enriched, 100% (COM, WAV); luminal A versus luminal B, 91.5%; and luminal B versus others, 91.1% (WAV, ARM, COM).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Bitencourt, 2020[11]	United State of America, Brazil, Austria	Retrospective study	311 patients	The machine learning models, which take into account clinical and radiomics MRI data, can be utilized to evaluate the level of HER2 expression and can make accurate predictions regarding pCR following neoadjuvant chemotherapy (NAC) for patients with HER2 overexpressing breast cancer.
Leithner, 2020[12]	USA, Germany, Italy, Mexio, Autralia	Retrospective study	91 patients	Evaluation of breast cancer receptor status and molecular subtyping can be performed with good diagnostic accuracy using radiomic signatures derived from diffusion-weighted imaging (DWI) in conjunction with apparent diffusion coefficient (ADC) mapping. When breast tumor segmentations could be carried out using ADC maps, researchers found that they acquired higher classification accuracies.
Leithner, 2019[13]	United State of America, Brazil, Austria	Retrospective study	143 patients	In this exploratory investigation, the use of radiomic signatures with CE-MRI made it possible to determine the breast cancer receptor status and the molecular subtypes with a high degree of diagnostic precision. These findings need to be backed up by more research with a larger sample size.
Granzier, 2021[14]	Netherland, Belgium, Germany	Retrospective study	292 patients	These findings point to the necessity of conducting reproducibility tests in order to preselect reproducible characteristics before conducting an accurate evaluation of the potential of radiomics.
Cain, 2019[5]	USA	Retrospective study	288 patients	In TN/HER2+ patients, the multivariate models that were based on pre-treatment MRI characteristics were able to accurately predict pCR.
Liu, 2019[15]	China	Retrospective study	586 patients	Based on the findings of the study, it was hypothesized that RMM could serve as a possible instrument for the development of a model that could predict pCR to NAC in breast cancer.
Xiong, 2020[16]	China	Retrospective study	125 patients	There is hope that a combination model that incorporates radiomics and clinical characteristics will be able to accurately predict drug-resistant breast tumors.

In the Leithner, et al (2019)[13] showed training dataset, radiomic signatures yielded the following accuracies > 80%: luminal B vs. luminal A, 84.2% (mainly based on COM features); luminal B vs. triple negative, 83.9% (mainly based on GEO features); luminal B vs. all others, 89% (mainly based on COM features); and HER2-enriched vs. all others, 81.3% (mainly based on COM features). In the separate validation dataset, radiomic signatures for luminal A versus luminal B (79.4%) and luminal B versus triple negative (77%) were effectively validated.

Granzier, et al (2021)[14] showed the radiomics features had no added value in predicting pathologic complete tumor response to neoadjuvant systemic therapy in breast cancer patients, nor did the combined models perform significantly better. They tentatively ascribe the lack of improvement in clinical models following the incorporation of radiomics to the effects of differences in acquisition and reconstruction parameters based on prior and current studies. Cain, et al (2019)[5] showed out of the 288 patients, 64 achieved pCR. The AUC values for predicting pCR in TN/HER+ patients who received NAT were significant (0.707, 95% CI 0.582–0.833, $p < 0.002$).

The radiomic signature that utilized multiparametric MRI was successful in reaching an AUC value of 0.79, making it the most accurate of the four radiomic signatures. In addition, the signature was successful in both the groups who tested positive for hormone receptors and negative for HER2, as well as the group that tested triple negative. In two out of the three external validation cohorts, RMM produced an AUC that was significantly higher than that of the clinical model. This difference was statistically significant.[15]

Last study with 125 breast cancer patients who had an MRI before receiving NAC. All patients underwent surgical resection, and the response to NAC was graded using the Miller-Payne grading system. Grade 1-2 instances were classed as NAC insensitive. The most recent study found that when paired with independent clinical criteria, the combined prediction model for identifying the Grade 1-2 group had higher discrimination power than the radiomic signature. The

validation cohort showed an area under the receiver operating characteristic curve of 0.935 (95% confidence interval [CI] = 0.848-1), and the decision curve analysis supported its clinical value.[16]

DISCUSSION

Breast cancer has the highest incidence among cancers in women worldwide Over the past decade, medical imaging technologies in clinical oncology have evolved from diagnostic tools to central players in personalized medicine. Solid tumors are spatiotemporally diverse.[1] Medical imaging, which can detect intra-tumoural heterogeneity non-invasively, has great potential. Medical imaging advancements with new hardware, imaging agents, and methods have allowed quantitative imaging in recent decades. Thus, image-based feature analysis must be automated and reproducible.[10,17]

Radiomics, the high-throughput extraction of picture features from radiographic images, overcomes this problem but needs more confirmation in multi-centric situations and in the lab.[10,17] MRI images were analyzed to determine HER2 expression level and pathologic response to NAC in breast cancer patients with HER2 overexpression. Bitencourt, et al (2020) findings indicate that MRI characteristics correlate with disparities in HER2 expression levels and pathological response to NAC. When machine learning models included both clinical and radiomic MRI parameters, the greatest accuracy was attained.[11]

Numerous studies have reported that pathological intratumor HER2 heterogeneity is associated with a poor prognosis. Most studies assess HER2 intratumor heterogeneity using both protein expression and gene signal from core needle biopsies collected at diagnosis. New approaches, however, have been proposed. Metzger Filho et al. took core biopsies from two distinct locations of each tumor (three cores/site) in 164 patients and classified intratumor HER2 heterogeneity as at least one area showing either HER negative or HER2 positivity by FISH in less than 50% of tumor cells.[18–20]

Even after stratifying by ER status and HER2 IHC, they discovered a link between intratumor heterogeneity and pathologic response.[19] Previous work has shown that MRI-based radiomic signatures can accurately classify breast cancer molecular subtypes.[12,13,21] Radiomics models that employ pretreatment MRI features to predict pCR following NAC have also been applied. Different models have shown pCR prediction accuracy rates ranging from 70% to 93% for triple negative and HER2 overexpressing subtypes.[5]

MRI-based model predicted pCR with an 83.9% accuracy among HER2 overexpressing tumors. Three radiomics metrics used to calculate pCR, variance, entropy, and zone level variance, are measurements of the spread of values inside the lesion, with larger values reflecting greater spread. Lesions with pCR had greater values for these metrics, indicating that increased radiomic heterogeneity benefits treatment response. Significantly higher 90th percentile values in pCR lesions appear to indicate that lesions with enhancement hotspots are more likely to respond well to treatment.[5]

The field of radiomics operates under the assumption that radiological images include more information than can be seen by the naked eye. Radiomics is a translational field of research that seeks to assist evidence-based clinical decision making by identifying connections between qualitative and quantitative information collected from medical imaging and clinical data. The workflow for radiomics consists of the following steps: images acquisition; images segmentation; features extraction; features selection; and model construction.[22,23]

CONCLUSION

Despite the fact that there is a great amount of methodological variation in each phase of the radiomics workflow, studies that focused on MRI-based radiomics for tumor response prediction to NST in breast cancer patients showed promising results.

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