BMC Cancer

SYSTEMATIC REVIEW

Open Access

Advancing personalized oncology: a systematic review on the integration of artificial intelligence in monitoring neoadjuvant treatment for breast cancer patients

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Abstract

Purpose Despite suffering from the same disease, each patient exhibits a distinct microbiological profile and variable reactivity to prescribed treatments. Most doctors typically use a standardized treatment approach for all patients suffering from a specific disease. Consequently, the challenge lies in the effectiveness of this standardized treatment and in adapting it to each individual patient. Personalized medicine is an emerging field in which doctors use diagnostic tests to identify the most effective medical treatments for each patient. Prognosis, disease monitoring, and treatment planning rely on manual, error-prone methods. Artificial intelligence (AI) uses predictive techniques capable of automating prognostic and monitoring processes, thus reducing the error rate associated with conventional methods.

Methods This paper conducts an analysis of current literature, encompassing the period from January 2015 to 2023, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Results In assessing 25 pertinent studies concerning predicting neoadjuvant treatment (NAT) response in breast cancer (BC) patients, the studies explored various imaging modalities (Magnetic Resonance Imaging, Ultrasound, etc.), evaluating results based on accuracy, sensitivity, and area under the curve. Additionally, the technologies employed, such as machine learning (ML), deep learning (DL), statistics, and hybrid models, were scrutinized. The presentation of datasets used for predicting complete pathological response (PCR) was also considered.

Conclusion This paper seeks to unveil crucial insights into the application of AI techniques in personalized oncology, particularly in the monitoring and prediction of responses to NAT for BC patients. Finally, the authors suggest avenues for future research into AI-based monitoring systems.

Keywords Breast cancer, Predicting complete pathological response, Neoadjuvant treatment, Artificial intelligence, Machine and deep learning

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Introduction

Millions of people succumb to cancer each year, marking it as one of the most devastating diseases. In 2018, around 2.1 million cases of breast cancer were diagnosed globally, accounting for almost a quarter of all cancer cases in women [1].

As Fig. 1 illustrates, BC is the most common cancer among women worldwide, according to the World Health Organization. In 2022, it made up about 23.8% of all cancer diagnoses made for female patients.

Breast cancer ranks as the second most prevalent cancer worldwide. Initially, a cancerous tumor remains confined to the duct or lobule of origin ('in situ'), often without causing noticeable symptoms and with a low likelihood of spreading (metastasis). Over time, this 'in situ' (stage 0) cancer can progress to infiltrate neighboring breast tissue, becoming invasive breast cancer, and then spread to neighboring lymph nodes (regional metastases) or to other organs in the body (distant metastases) [2, 3]. When a woman dies of breast cancer, it means that the cancer has metastasized to various parts of the body, resulting in a generalized form of cancer.

Breast Cancer is the main reason that makes women die because of cancer in big numbers. It can fortunately be treated by detecting it early and giving treatment soon. These techniques include employing medical imaging such as MRI or PET scans together with artificial intelligence methods hence they facilitate in such areas as breast cancer diagnosis, monitoring its progress or planning for its treatment. Hormone receptor Her2 subtype for breast cancer is one of the well-known ways it is classified taking note of human epidermal growth factor receptor 2 hormone receptors presence or absence [4–7]. Hormone receptors are defined as proteins present on the surface of breast cell that respond to estrogen and progesterone, two hormones capable of promoting the growth of specific types of breast cancers. Additionally, HER2 is a protein that can stimulate the growth of breast cancer cells. This classification system aids doctors in determining the most suitable treatment plan for each patient. The HR/HER2 subtype further categorizes breast cancer into four distinct subtypes:

- ➢ HR-positive/HER2-negative: This subtype represents the most common form, constituting approximately 70% of all breast cancers. These cancers exhibit estrogen and/or progesterone receptors but lack HER2. Treatment typically involves hormone therapy, which hinders the effects of estrogen and/or progesterone on cancer cells.
- ➢ HR-positive/HER2-positive: This subtype encompasses roughly 15–20% of all breast cancers. These cancers possess estrogen and/or progesterone receptors, along with an excess of HER2 protein on the cancer cell surface. Treatment usually involves a combination of hormone therapy and targeted therapy to block the HER2 protein.
- ➢ HR-negative/HER2-positive: This subtype makes up about 5–10% of all breast cancers. These cancers lack estrogen or progesterone receptors but have an abundance of HER2 protein on the cancer cell surface. Treatment typically involves targeted therapy to inhibit the HER2 protein.

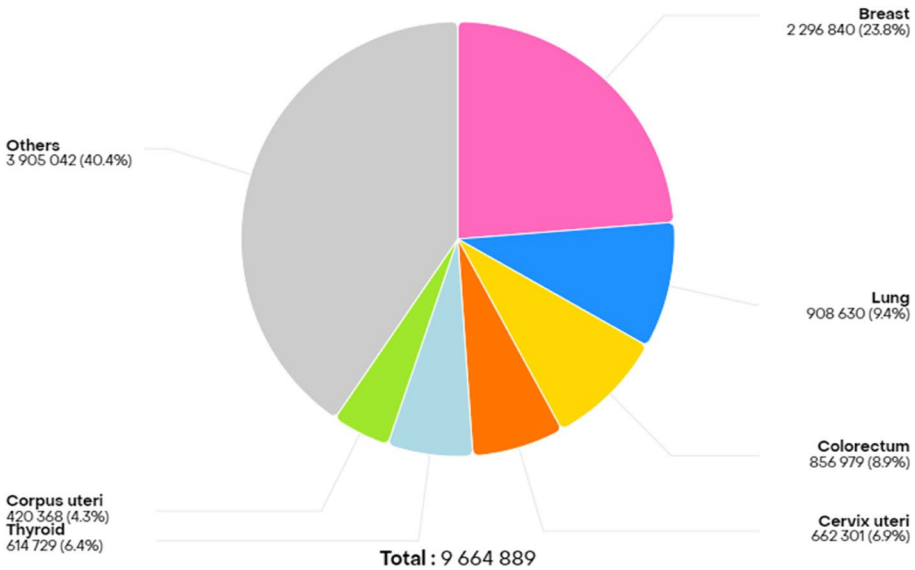

Fig. 1 The absolute incidence of breast cancer among females in 2022

➢ HR-negative/HER2-negative: Also known as triple-negative breast cancer, this subtype accounts for around 10–15% of all breast cancers. These cancers lack estrogen, progesterone, and HER2 receptors. Treatment generally involves chemotherapy.

BC treatment includes several therapies: surgical operation, radiation treatment, drug curing, hormonal regulation, targeted treatment [7]. Typically, before the surgery for BC, neoadjuvant chemotherapy (NAC) is mainly used with an additional purpose of reducing its size hence lowering chances of a distance spread [8, 9]. This technique is very useful for improving the effectiveness of surgery results, which in potential may be useful for breast saving in cases such as non-resectable tumors or total mastectomy [10]. In the neoadjuvant treatment of high-risk, early-stage BC, a full pathologic response (PCR) is reached when there is no longer any evidence of disease, potentially serving as a substitute endpoint to evaluate its long-term results [11, 12].

The ability to track an individual's response to NAC over time and assess the likelihood of a positive response at the outset of treatment holds significant clinical importance. This capability could aid in minimizing unnecessary NAC toxicity and adjusting treatment regimens dynamically to enhance overall effectiveness. In order to interpret massive amounts of data for computer-aided medical and surgical procedures (including planning and intervention) and to enable non-invasive quantitative assessments, medical imaging is essential for decision-making and diagnosis. It makes internal features visible that are hidden from view from the outside of the patient. Various modalities contribute to medical imaging [3, 13, 14], including mammography, MRI, Ultrasound, CT scan, and others.

Radiomics, which involves the extraction of quantitative information from medical imaging data, is an emerging field in the realm of medical imaging [15, 16]. In recent years, artificial intelligence [17] has become more and more common, especially in the medical industry. Through machine learning, which is increasingly common in image classification and prediction, it has aided the creation of systems enabling diagnosis, prognosis [18], and medical treatment planning. Furthermore, the most popular type of deep learning [19–22] allows models with numerous processing layers to learn data representations at different levels of abstraction. These techniques have impacted many other domains, by substantially advancing the state of the art in speech recognition, visual object recognition, and object detection [23–25], including drug prescription and biomedicine [26–28].

The aim of this work was to provide a reliable and comprehensive summary of the results of previous studies. By offering relevant information on research that merges artificial intelligence and medicine, the aim was to facilitate the study of cutting-edge discoveries and recent breakthroughs. Particular emphasis was placed on personalized oncology, including the monitoring of breast cancer patients undergoing neoadjuvant treatment.

Our contribution

Table 1 summarizes closely related surveys/reviews on breast cancer monitoring and reveals our survey's novelty. The aforementioned investigations and analytical work concentrated on a specific imaging modality, such as MRI [29], PCR prediction, or deep learning approaches [30, 31]. Our study differs from previous studies in that it focuses on different imaging modalities (MRI, US, etc.), presents some public datasets used for PCR prediction, and employs AI techniques for PCR prediction, axillary lymph node status prediction, and breast cancer molecular subtype prediction.

Based on the Table 1 and the above considerations, the main contributions of this survey are summarized as follows:

- To summarize previous work, guide and facilitate the research process for new and all researchers, and reveal important information about the use of artificial intelligence techniques in monitoring and predicting response to neoadjuvant therapy for breast cancer patients including statistical, radiomic, Machine and Deep Learning methods and hybrid models.
- To present different types of imaging modalities as well as MRI, US, CT Scan, etc. and several public datasets concerning the prediction of response to neoadjuvant therapy.
- To discuss several challenges, limitations, and future directions concerning applications of AI techniques in personalized medicine to follow breast cancer patients.

The rest of the document is structured as follows. Section III describes the research methodology used. Section IV includes tables describing previous studies on predicting response to neoadjuvant therapy using the PRISMA methodology, the types of modalities available and the publicly available datasets. Section V discusses each work in detail, highlighting some of the issues that make AI deployment in medicine difficult, also the limits of the works chosen. Section VI presents the conclusion and future directions.

Table 1 Comparative analysis of our work and existing review/survey studies

Ref	Year of Pub	Search duration	PCR prediction	Axillary lymph node status prediction	Prediction of molecular subtypes of breast cancer	Image modality included	Datasets presentation	Methodology included	Review/Survey focus
[29]	2022	until 12–2021	Yes	No	No	MRI	No	ML, DL, and radiomics	They focused on the diagnostic accuracy of ML and DL models with MRI in predicting pathological response to neoadjuvant chemotherapy in breast cancer patients and a comparison between them
[30]	April 2023	2012 until 2022	Yes	No	No	All	Yes	DL	They present a comprehensive overview of investigations on mammography, ultrasound, magnetic resonance imaging, and digital pathology images conducted over the previous ten years as part of deep learning-based breast cancer imaging research
[31]	November 2022	2015 to 1 Nov 2022	Yes	No	No	MRI	No	DL	This study aims to perform a systematic review of deep learning methods that use MRI images to predict PCR in breast cancer
[32]	May 2022	Until 2021	Yes	No	No	MRI, CT scan	No	DL, ML	The aim is to evaluate studies of how effectively AI predicts outcomes for patients receiving treatment for breast cancer

Table 1 (continued)

Ref	Year of Pub	Search duration	PCR prediction	Axillary lymph node status prediction	Prediction of molecular subtypes of breast cancer	Image modality included	Datasets presentation	Methodology included	Review/Survey focus
Our study	-	2015–2023	Yes	Yes	Yes All kinds of image modalities		Yes, in this study we present some public datasets concerning the prediction of response to the neoadjuvant treatment	DL, ML, Statistics, radiomic, and hybrid models	Personalized oncology i.e. monitoring and predicting response to neoadjuvant treatment for breast cancer patients based on all kinds of modalities and different IA techniques

Survey methodology

Search strategy

For this study, we will elaborate on the following search strategy to identify relevant literature.

- This search strategy has been adapted to the database: Scopus, MEDLINE
- The search terms used are (Monitoring) AND (Breast cancer AND Neoadjuvant AND treatment) AND (Prediction) AND (Artificial Intelligence OR Machine Learning OR Deep Learning). Figure 2 displays a word cloud created from the selected papers for this systematic review. Common phrases such as "breast", "cancer", "response", "neoadjuvant", and "chemotherapy" suggest that response prediction is a major area of research for breast cancer treatment, especially when it comes to Neoadjuvant Chemotherapy. Additional terms "MRI" and "deep learning" emphasize potential importance of automated learning techniques and medical imaging technologies in the studies mentioned here. This word cloud provides a map of what research currently endeavors to do in laying out its goals and priorities, given the set of trends and key issues identified in the literature.
- Search duration: All searches were carried out between 2015 and January 2023.
- Article types: Research articles, Conference papers
- Language: English only
- Countries: all

Selection criteria

Selection criteria will be based on the PRISMA methodology [33]. The main objective of the search is to determine the existing literature on "breast cancer follow-up". The search will cover the years 2015 to 2023 and all countries.

Research quality assessment

The review will be based solely on original research articles and conference papers. To maintain the quality of the review, all duplicates will be carefully checked. Article abstracts will be thoroughly checked for article analysis and purification to ensure the quality and relevance of the academic literature included in the review process. Each research paper will be thoroughly evaluated. Other exclusion criteria Articles published in languages other than English will be excluded from the study, as well as duplicates.

Study selection process flowchart

The PRISMA diagram is seen in Fig. 3. In this study, 25 papers were chosen for a comprehensive analysis.

Results analysis

The search strategy described above identified 25 articles out of 102, in general, with regard to the inclusion and exclusion criteria. Figure 4 shows the number of studies selected on the prediction of complete pathological response for breast cancer patients treated with chemotherapy over the last 8 years. Figure 5 shows that, of the articles selected, 12% were conference papers and 88% were journal articles. Figure 6 shows a detailed breakdown of the sources of the publications reviewed from a variety of major publishers. The majority of papers, 35%, came from different type of publisher like PLOS, AMA, etc. Springer contributed 12% of publications, while IEEE Xplore contributed 11%. Elsevier accounted for 9% of all publications. The bioRxiv preprint server contributed 6% of articles, reflecting the latest research trends. Other notable contributions include Wiley, BioMed Central and Nature, each of which contributed a small proportion of articles, reflecting the wide range of sources used in this study.

Summary of the approaches used in the selected studies

Tables 2 and 3 summarize previous work on the prediction of complete pathological response in breast cancer using deep learning, machine learning and statistical models.

Type of clinical data available and example of open-access datasets

Clinical data is a description of details such as the diagnosis, treatment and impact of breast cancer on the patient, which can be used for research and analysis [56]. Types of clinical data include:

- ✓ Pathology reports, which provide information on the type and stage of cancer based on analysis of tumor tissue samples.
- ✓ Imaging results, such as mammograms, ultrasounds, or MRIs, which visualize the size and location of the cancer.
- ✓ Treatment records, which detail the types of therapies, received by the patient, such as surgery, radiotherapy, chemotherapy, or hormone therapy.
- ✓ Follow-up information, which tracks the patient's progress after treatment, including the risk of recurrence and overall survival.

Multipara metric MRI data

Multiparametric magnetic resonance imaging (mpMRI) is a medical imaging technique that combines several MRI sequences to obtain a detailed view of tissues. Multiparametric MRI data typically include T1-weighted,

Fig. 2 Keyword density in the articles included in the review

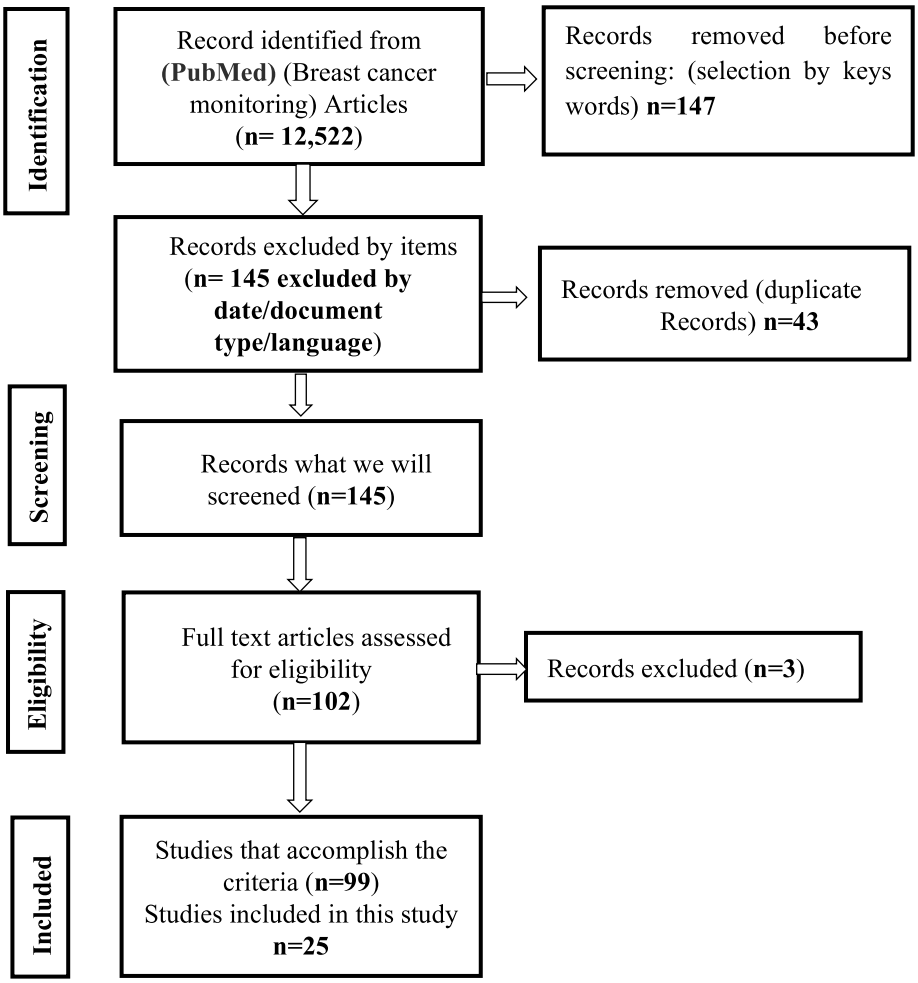

Fig. 3 PRISMA flow chart

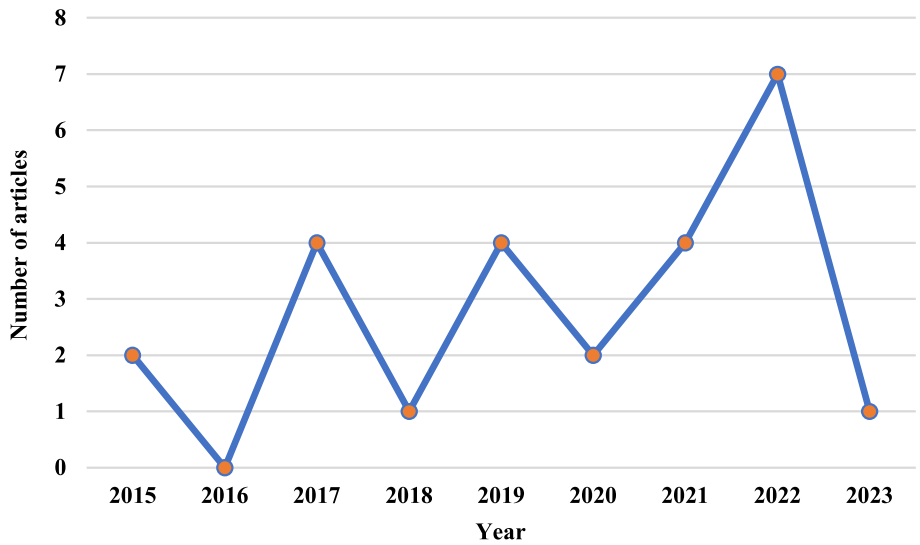

Fig. 4 The number of the publication selected per year

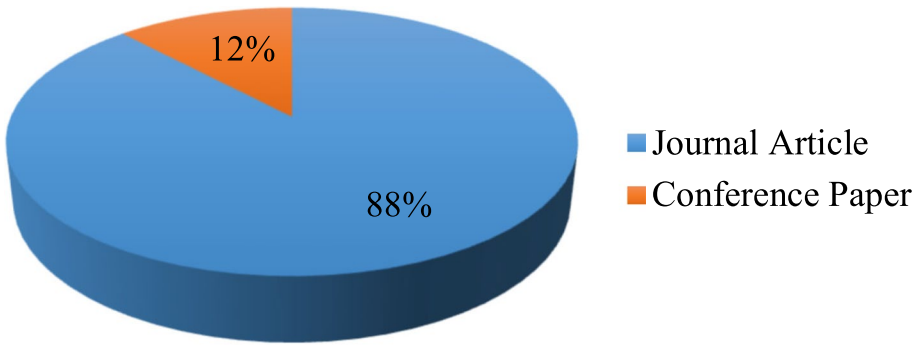

Fig. 5 Percentage of publications by publication type

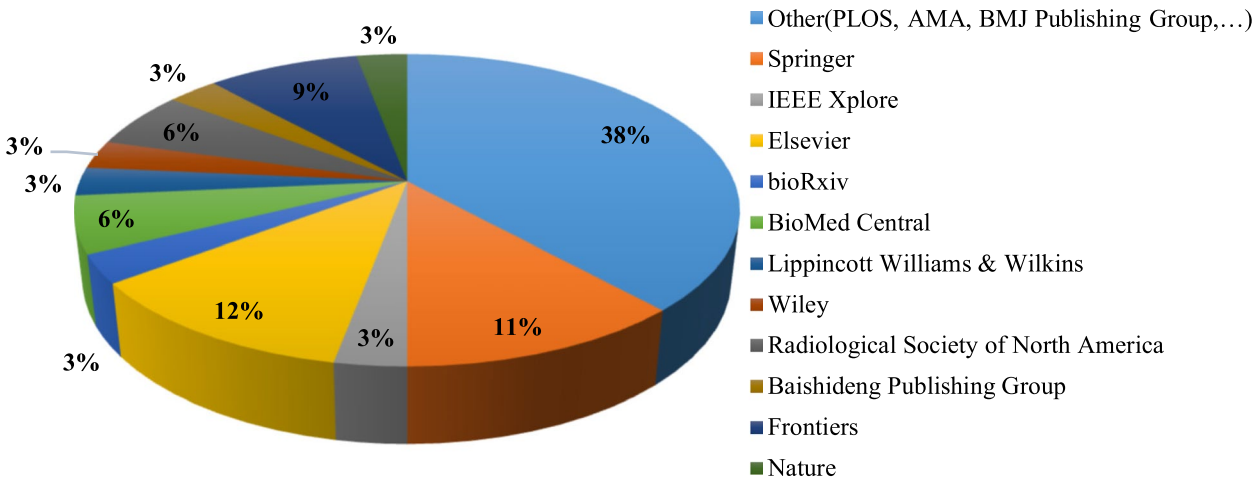

Fig. 6 Percentage of selected papers per publishers

Table 2 Summary of previous work in predicting response to neoadjuvant treatment for breast cancer using DL models

Study	Date	Dataset/size	Data type (imaging/non-imaging)	Multiple centers	Models	Multiple points	Augmented Data	AUC	Accu
Hongyi Dammu [34]	2020	I-SPY TRIAL1 level 3/ 155	MRI-DCE + Non MRI	Yes	CNN	Yes	No	0,83 ± 0,03	0,81 ± 0,03
Mohammed El Adoui [35]	June 2020	Private /42	MRI-DCE	No	CNN	Yes	Yes	0,91	
Benjamin Q. Huynh [36]	March 2017	Private /64	MRI-DCE	No	VGGNet + LDA	Yes	No	0,85	
Peng [37]	2022	Private /356	MRI -DCE + Non MRI	No	ResNeXt50	No	Yes	0.83	77,2%
Richard Ha [38]	October 2018	Private/141	MRI	No	CNN	No	Yes	___	87,7% ± 0,6%
Sunghoon Joo [39]	September 2021	Private /536	MRI (T1W, T2W) + Non MRI	No	ResNet-50	No	Yes	0,88	85%
MariaColomba [40]	July 2021	I- SPY TRIAL 1/134	MRI -DCE + Non MRI	Yes	CNN	Yes	No	0,90	92,3%
Li, F [41]	August 2021	Private/540	Histological images	No	DL based on Inception v3	No	No	0,84	85,3%
Xie J [42]	April 2022	Private/ 114	Ultrasound images	No	DBNN	Yes	No	0,97	87,5%
Meng Jiang [43]	April 2021	Private/592	Ultrasound images &Clinical	Yes	DLRN (Based on DenseNet-201 and RL)	Yes	No	0,94	83,9%
Bao Li [44]	October 2022	Prvate/874	Histological images &Clinical	Yes	DLPCM (based on ResNet18)	Yes	No	0.78	
Hongyi Duanmu [45]	August 2022	Prvate/73	Histological images (H&E) & immunohistochemistry (IHC)	No	ResNet-34	No	No		93%

T2-weighted, diffusion-weighted imaging (DWI) [57] and dynamic contrast-enhanced imaging (DCE) sequences [57]. T1- and T2-weighted images provide information about tissue anatomy and structure, while DWI provides information about the diffusion of water molecules in tissue. DCE imaging involves the injection of a contrast agent to identify blood vessels and blood flow in tissues. Multiparametric MRI data are commonly used for cancer diagnosis, prognosis and treatment monitoring. In the literature, works [35, 36, 47] have used multiparametric MRI data.

Ultrasound data

Ultrasound used high-frequency sound waves to create breast-tissue images for study purposes regarding detection possibilities. The data on breast cancer in ultrasonography typically consists of lumps or lesions that are suspected to be malignant as well as additional distinguishing features like location either textural or morphological differentiations from benign tumor (not cancerous). This type of information had been exploited in the following studies; [22, 42, 43, 51].

Non-imaging data types

These include molecular subtypes, demographic, genetic, and other data. They include clinical notes, radiological reports, and pathological reports [58]. Some clinical variables used in previous work [58]: Age at diagnosis, Estrogen receptor, Progesterone receptor, Human epidermal growth factor receptor, and Clinical grade before treatment.

Histological image data

Histological image data refers to tissue images obtained by histological techniques, such as hematoxylin staining to stain nuclei blue-violet and eosin staining to stain cytoplasm and other components pink, which are used to visualize tissue structure and composition at a microscopic level. They contain microscopic histopathological information about the tumor that can be used to identify different cell types and guide diagnosis and treatment [59, 60]. Works [41, 44] are based on this type of data.

Figure 7 below summarizes the different imaging modalities.

Table 3 Summary of previous work in predicting response to neoadjuvant treatment for breast cancer using ML models and statistics

Study	Date	Dataset /size	Data type (imaging/non-imaging)	Multiple centers	Models	Multiple points	Augmented Data	AUC	Accu
Syed A [46]	2023	BMMR2 Challenge/ 117	MRI (DCE-DWI) + Non-MRI	Yes	XGBoost	Yes	No	0.95	—
Amirhessam Tahmassebi [47]	2019 February	Private/38	MRI + Non-MRI	No	XGBoost, SVM, LDA, LR, RF, SGD, Decision Tree, and AdaBoost	Yes	No	0,94	
Elizabeth Hope Cain [48]	October 2018	Public (BMMR2)/288	MRI -DCE	No	SVM, RL	Yes	No	0,70	
Ke ZR [49]	April 2022	Private /487	Non MRI	No	SVM, RF, NB, ANN, DT, GLM	No	No	0.96	
Aghaei F [50]	October 2015	Private/68	MRI	No	ANN, Merging feature	Yes	No	0,96	
Zhou T [51]	October 2022	Private /247	Ultrasound images, clinical and pathological information	Yes	Nomogram & RF	Yes	No	0,76 &0,85	
DiCenzo [52]	29 June 2020	Private/82	Quantitative Ultra Sound images	Yes	KNN	No	No		87%
Xiong, Q [53]	April 2019	Private /125	MRI (DCE-MRI, T2WI, DWI) + clinical characteristics	No	LR	No	No	0,93	93.55%
Kotaro Yoshida [54]	October 2022	Private/78	DCE-MRI + clinical data	No	RF	Yes	No	0,77	80%
Braman [55]	May 2017	Private /117	DCE-MRI	No	LDA,DLDA, QDA, Naïve Bayes, SVM	No	No	0,83	79%

Examples of open-access datasets

"I-SPY 1/ACRIN (American College of Radiology Imaging Network) 6657 trials (ISPY1)" This dataset contains 222 patients from May 2002 to March 2006 at nine institutions [32]. The localization scan and T2-weighted sequence were followed by a contrast-enhanced T1-weighted series as part of the image acquisition process. Four separate time intervals were covered by MRI tests to assess the patient's response to therapy and the likelihood of recurrence.

"I-SPY2 trial / ACRIN 6698" The ACRIN 6698 database of the I-SPY2 trial is a simultaneous multipara-metric MRI dataset of the breast to predict response to NAC-2 (BMMR2) [62].

In this study [63], the aim was to determine whether a change in the Apparent Diffusion Coefficient (ADC) of the tumor on Diffusion-Weighted (DW) MRI is predictive of a pathologically complete response (PCR) to neoadjuvant chemotherapy for breast cancer. They detailed how the data was collected, investigated whether lesion subtypes influence the predictive value of ADC, and showed the performance of tumor ADC changes in predicting PCR at each treatment time point.

272 patients made up this multicenter data cohort between August 2012 and January 2015. MRI scans were performed at four treatment time points (pre-treatment (T0), early treatment after 3 cycles of paclitaxel (T1), intermediate treatment between paclitaxel and anthracycline (T2), post-treatment (T3)).

Inclusion criteria:

✓ Age ≥ 18 years
✓ Non-pregnant and non-breastfeeding
✓ Invasive breast cancer of 2.5 cm or more confirmed on clinical examination or imaging and who were planning to undergo neoadjuvant chemotherapy
✓ Any HR/HER2 tumor status

Exclusion criteria:

✓ Patients with distant metastases

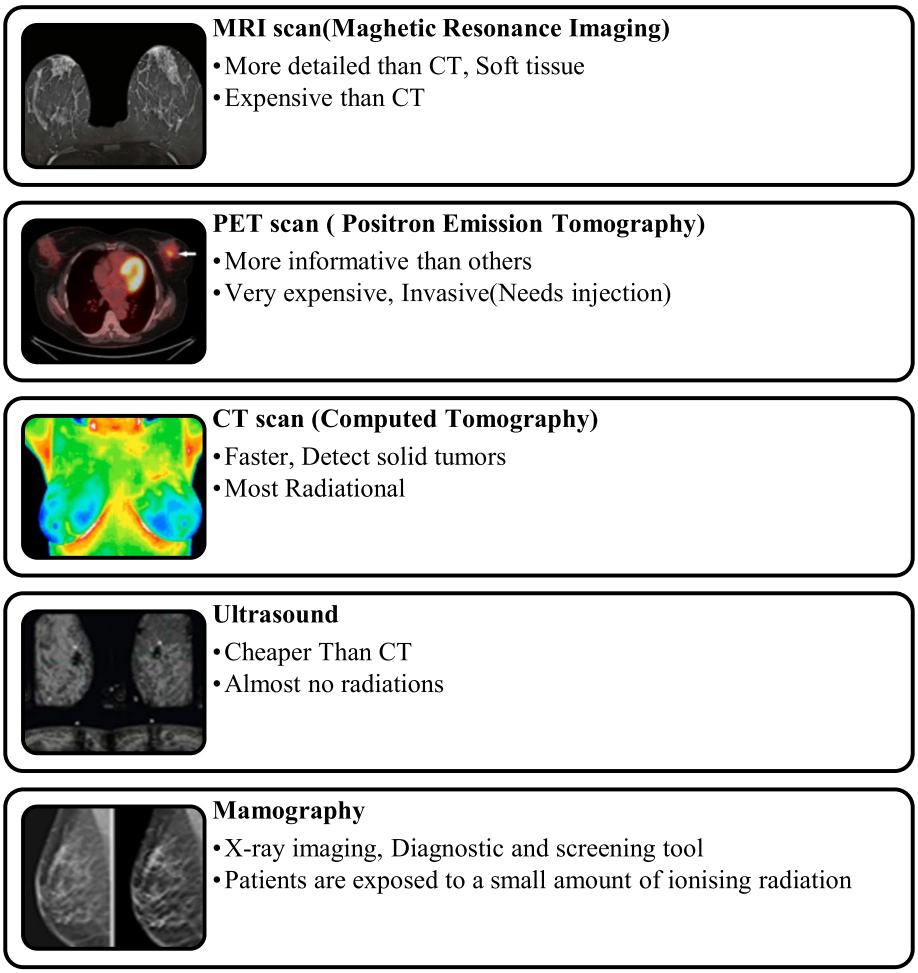

Fig. 7 Breast cancer imaging techniques [61]

✓History of allergic reactions attributed to compounds of similar chemical or biological composition to the study agent or accompanying supporting drugs.
✓ Use of any other investigational agent within 30 days of initiation of study treatment.

"Duke Breast Cancer MRI dataset" The Duke Breast Cancer MRI dataset is a unique retrospective institutional collection of 922 DCE-MRI sequences and clinical data from patients with biopsy-confirmed invasive breast cancer that were collected at Duke Hospital between 2000 and 2014 [64, 65].

Exclusion criteria:

✓ Patients with prior breast surgery
✓ History of breast cancer
✓ Neoadjuvant therapy before the MRI acquisition

"QIN-Breast" The 68 patients in the dataset were scanned using longitudinal PET/CT and quantitative MR at three different time points [66, 67]: at the beginning of treatment (t1), after the first cycle of treatment (t2), and at the end of all treatments (before surgery) (t3). The MRI data consists of multi-flip data for T1 mapping, diffusion-weighted images (DWIs), and DCE-MRI. Additionally, labels for patient-level treatment responses (pCR/non-pCR) have been assigned to monitor how well treatments are working.

Figure 8 shows the frequency of use of these four data sets in the literature.

Discussion

Comparative analysis using deep learning models

This section presents the contributions of researchers in recent years for predicting pathological complete response (PCR) in breast cancer through deep learning techniques.

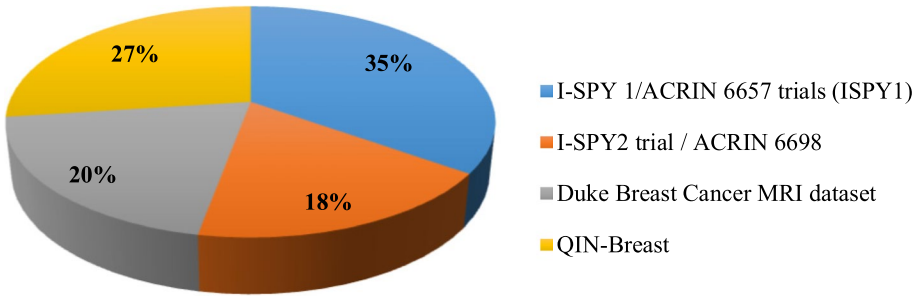

Fig. 8 The frequency usage of datasets

Hongyi Dammu [34] has developed an innovative CNN (Convolutional Neural Network) deep learning model to predict PCR, RCB (Cancer Residual Burden), and PFS (Progression-Free Survival) using multiparametric MRI data (dynamic contrast-enhanced (DCE) and T2-weighted MRI as three-dimensional whole images without the need for tumor segmentation), demographics, and molecular subtypes in breast cancer patients treated with neoadjuvant chemotherapy to plan medical treatment. Using data from 155 patients at non-concurrent times, they trained their model with five-way cross-validation. They further evaluated the both models stack and concatenation w.r.t to each other. They also found their model outperformed both stack and concatenation models with AUC's of 0.83 and 0.61, respectively. These results were obtained exactly at two specific treatment points; four weeks before the start of anthracycline-cyclophosphamide chemotherapy after the last chemotherapy treatment and before surgery (pre6 and post-NAC).

Mohammed El Adoui [35] developed a novel CNN deep learning model that was based on multiple MRI inputs (MRI-DCE) before NAC to predict breast cancer response through neoadjuvant chemotherapy (classifying whether patients have PCR or non-PCR). Among the techniques used in this work were data pre-processing; the volume of each tumor in the image was cropped by making a box surrounding the volume of interest (VOI) and the application of 3D affine registration to align the imaging data and since they arranged only 42 patients they applied data augmentation (rotation, translation, and zoom). To test the proposed model, an external cohort of 14 cases was used. An AUC value of 0.91 was obtained.

In Benjamin Q. Huynh [36] work, the aim was to predict the response to NAC based on contrast time points of breast DCE-MRIs and assess their importance. MRI features were extracted using a pre-trained CNN model and then used in a linear discriminant analysis classifier to predict response to NAC. The AUC value of the LDA classifier trained on pre-contrast time point features was 0.85, which was the best result when compared with other classifiers that were trained on other time point features (AUC from 0.71 to 0.82). They concluded that the pre-contrast period was the best predictor of response to treatment.

Peng [37] examined how well radiomic analysis and deep learning performed in predicting PCR based on MRI-CDE prior to breast cancer treatment. They employed multilayer perceptron (MLP) for deep learning and linear discriminant analysis (LDA) as a classifier for radiomic analysis in order to rank the efficacy of NAC treatment.

They found that the performance of the DL model based on pre-treatment MRI-DCE was AUC = 0.83, which was superior to the radiomic analysis model which had AUC = 0.755. They concluded that the deep learning model outperformed linear discriminant analysis.

The aim of Richard Ha [38] study was to develop a new CNN to predict response to NAC using an MRI data set and pathological confirmation of response to treatment. This model was trained on a dataset of 141 patients divided into 3 subgroups according to their response to NAC: complete pathological response, partial response and no response. The aim of this work is to guide appropriate therapy in non-responders, minimize the toxicity of ineffective treatments and facilitate the use of new-targeted therapies such as neoadjuvant therapy. They used cross-validation five times, so they applied data augmentation (random affine transformation, random rotation, horizontal flip, and zoom) and L2 regularization to reduce the over-fitting problem. The results obtained were 88%, 73.9%, and 95.1% as overall accuracy (Accu), sensitivity, and specificity values respectively.

Sunghoon Joo [39], developed a multimodal DL model (CNN) based on pre-treatment MRI features (T1-weighted subtraction (T1W) images and T2W images) and clinical information. The dataset contains 133 and 403 patients with and without PCR respectively, focal loss was used to address the imbalance problem.

The dataset was divided into two; 429 patients for training and 107 for validation. Data augmentation was applied to improve model generalization. They created the architecture of a deep neural network that combines ResNet-50 with 3D CNNs for MRI images and fully connected (FC) layers for clinical information. This model scored 0.888 for AUC, 85% for accuracy, and 93.2% for specificity.

In this study, Maria Colomba [40] proposed a transfer learning model with DCE-MRI and selected clinical features (ER, PgR, HER2, and molecular subtype) to predict the pathological response of patients to NAC (PCR or Non-PCR) to assess the efficacy of NAC before the end of therapy. They used a pre-trained CNN to extract features automatically from DCE-MRIs to design an SVM (Support Vector Machine) on the most stable and optimal features to classify pathological responses. The set of tuning data used for the selection of important features comprises 108 patients; the model obtained an accuracy of 91.4% and an AUC of 0.93. The test data set used contains 26 patients, and the result obtained on this was 92.3% and 0.90 for accuracy and AUC respectively.

In this paper, Li, F [41], used a DL model based on histopathological information on tumor biopsy images i.e. information extracted from hematoxylin and eosin-stained tissue images to propose a new biomarker that has the PCR score to improve prediction of PCR to neoadjuvant chemotherapy. They defined PCR as the absence of residual invasive disease in the breast and lymph nodes. In total, they recruited a set of 540 patients, who were divided into 429 patients as training data and 107 test data. Biomarker generation was based on the Inception V3 deep learning architecture. They have an AUC = 0.847 and accuracy = 85.3%. They established that PCR score correlated independently with PCR, so PCR score was a promising biomarker that can classify breast cancer patients as responders or non-responders based on H & E stained images alone.

The aim of this study Xie J [42], was to introduce a new Deep Learning model named double-branch convolutional neural network (DBNN) based on ultrasound images at different treatment times (before and after the first stage of chemotherapy) to predict NAC PCR in patients with locally advanced breast cancer. They defined PCR as the absence of residual invasive carcinoma in the breast at the time of surgical resection. Ultrasound video data from 104 women with locally advanced breast cancer were recruited, after which they sliced them to form and select high-quality images in the pre-processing stage based on selecting regions of interest and applying a few filters such as the median filter. The DBNN model was based on feature sharing and weight assignment to predict PCR at NAC. The feature sharing or merging method adopted was the sum of feature elements that has the advantage of directing the model to take into account correlations between data at different stages of NAC during training. The first and second branches of the model were designed for feature extraction of the data before NAC and after the first stage of NAC respectively. It has an area under the curve of 0.972 and an accuracy of 87.5%.

Meng Jiang [43], In this paper, they developed a deep learning radiomic nomogram (DLRN) based on radiomic features extracted from ultrasound (US) and clinical images to predict response to NAC in Locally Advanced Breast Cancer patients. They merged the 64 features extracted by the DenseNet201 architecture with 479 radio mic features (histogram, morphology, intensity, laws, wavelets, and texture) manually extracted by software. They then selected the relevant features to construct radiomic signatures for the pre-and post-processing data and concatenated them with the clinical data. Afterward, they used multivariate logistic regression (LASSO) to select independent predictors of PCR from the radiomic signatures and significant clinical features. Finally, they constructed the nomogram to predict the probability of PCR. Their AUC = 0.94 and accuracy was 83.9%.

Bao Li [44], in this paper, built a Deep Learning model to predict PCR using whole slide images (WSI: after microscopic examination of hematoxylin and eosin (H&E)-stained tissue; these stained tissues were digitized as whole images). They built a patch-level classifier based on pre-trained ResNet18 to determine the category of each patch: cancer cell-predominant patches or stromal cell-predominant patches. A multivariate logistic regression model with tenfold cross-validation was performed using the 11 features selected from the results of the ResNet18 classifier for PCR prediction. This pathological deep learning model obtained an AUC of 0.71. They built a multivariate logistic regression (MLCM) clinical model on the clinical information and obtained an AUC of 0.76. After combining the two models (DLPM and MLCM) to build a pathological clinical deep learning model (DLPCM), this model had an AUC of 0.78, outperforming the other models.

Hongyi Duanmu [45], In this study, they developed a method based on a deep learning model to predict the response of triple-negative cancer patients to NAC therapy using a variety of serial pathological images stained with hematoxylin and eosin as well as two immunohistochemistry biomarkers (Ki67 and PHH3). Then, they introduced the spatial attention mechanism [68] to focus the system's attention on regions enriched with tumor cells that were positive for the Ki67 and PHH3 biomarkers. Finally, they trained ResNet-34 to predict PCR. They started by using the Mask-RCNN model [69, 70] to detect

tumor cells. Next, they used color conversion [71] to generate the Ki67 and PHH3 biomarkers. They used a private dataset of 73 patients to test their method, and they got a 93% accuracy rate.

Comparative analysis using machine learning models and statistics

This section presents some recent contributions in the field of machine learning for PCR prediction in breast cancer.

Syed A [46] used an eXtreme Gradient Boosting (XGBoost) machine learning model to predict PCR of breast cancer patients for neoadjuvant chemotherapy, using multiparametric (DCE and DWI) and non-imaging MRI data (demographic and molecular subtype data: age, lesion type, race, hormone receptor status…) at different time points. They used the Gray-Level Co-occurrence Matrix (GLCM) to extract texture features from MRIs to train the XGBoost model on these extracted GLCMs and non-imaging data to predict PCR. The total number of features used was 372; 360 GLCM features. Combined with six features from non-imaging patient data and six features extracted from the ADC (apparent diffusion coefficient) parametric map. Despite having a large number of features, they did not apply feature selection methods to reduce them, as XGBoost intrinsically selects the most important features. The database used in this study contains missing data, so they filled in these values with the next patient values; this is the backfill method, as well as the minority oversampling technique (the minority class was PCR) to balance the dataset. This model has an AUC of 0.951.

The aim of this paper Amirhessam Tahmassebi [47], was to evaluate the potential and feasibility of machine learning models with multi-parametric MRI (T2-weighted MRI, DCE MRI, and DWI) for early prediction of PCR to NAC, RFS, and Disease-Specific Survival (DSS) in breast cancer patients. The models evaluated were SVM, LDA, LR (Logistic Regression), RF (Random Forest), SGD, decision tree, AdaBoost, and XGBoost. They were based on recursive feature elimination to show the importance of each feature used. XGBoost outperformed the other models in PCR and DSS prediction with AUC = 0.943 and AUC = 0.92, respectively, but for RFS prediction the LR model showed better performance with AUC = 0.866. On the other hand, the XGBoost model showed a higher and more stable performance when compared to the other models for the prediction of PCR, RFS, and DSS.

Elizabeth Hope Cain [48] used two ML models (SVM, RL) to predict PCR based on features extracted from DCE-MRI in patients with breast cancer and in particular in patients undergoing neo-adjuvant therapy (NAT), neo-adjuvant chemotherapy (NACT), neo-adjuvant therapy in patients with TN/HER2 + cancer subtype. In this work, PCR was defined as the absence of residual invasive or in situ disease in the breast or lymph nodes, and Non-PCR as any residual invasive disease in the breast or lymph nodes. They divided the data set into two equal groups, one for learning and the other for testing. They selected just 12 features based on multilinear regression. The SVM model outperformed logistic regression by an AUC value of 0.707 in predicting PCR in TN/HER + patients who received NAT. They, therefore, found that SVM was the most robust in predicting response to NAC.

Ke ZR [49], tried to develop new models for predicting response to NAC (NAC and Non-RNAC) in breast cancer patients using pre-treatment serum lipids and markers of serum inflammation, based on ML models. The models used in this study were SVM, RF, NB (Naive Bayes), NN (Neural Network), DT (Decision Tree), and GLM (Generalized Linear Model). After applying a feature selection technique that was multivariate logistic analysis on 24 candidate demographic variables to identify the most optimal, they were chosen only 12 factors included in the ML models. The performance of the models was as follows: the SVM model performed best (AUC = 0.96), which gave almost similar results to the RF model (AUC = 0.94), superior to the NB model (AUC = 0.86), the NN model (AUC = 0.88), the DT model (AUC = 0.83) and the GLM (AUC = 0.81).

Aghaei F [50] have proposed two approaches: the feature fusion method and an ANN (Artificial Neural Network) classifier-based approach, which relies on image kinetic features calculated from breast MRI images acquired before and after chemotherapy, to predict PCR. This study aimed to identify a new clinical marker potentially useful for quantitatively predicting PCR. The dataset comprised 68 patients, including 25 PCR and 43 Non-PCR. The researchers extracted 39 features from the MRIs and then used an attribute-based classifier to select 12 optimal features that offered the best classification performance. The feature fusion approach resulted in an AUC of 0.85, and the ANN classifier approach resulted in an AUC of 0.96.

The aim of this study DiCenzo [52] was to predict response to NAC in patients with locally advanced breast cancer using quantitative ultrasound radiomics, which has been used in several clinical studies [52]. They performed a texture analysis using a gray-level co-occurrence matrix on the six quantitative ultrasound spectral features that were extracted from the normalized power spectrum. They used a private dataset of 82 patients.

They used three machine learning approaches including SVM with radial basis function kernel, Fisher's linear discriminant, and K-nearest neighbor which obtained the best performance among them, it has an accuracy of 87%.

Zhou T [51], this work aimed to predict axillary lymph node status (lymph node PCR) after neoadjuvant therapy (NAT) based on clinicopathological and ultrasound information during NAT using the nomogram and random forest method to avoid axillary lymph node dissection. They used three types of information as model inputs: clinical information (age and pre-NAT T and N clinical stages), pathological information (ER, PR, HER2, Ki-67), and ultrasound information (maximum diameter of the primary lesion, maximum diameter of suspicious lymph nodes in each cycle and lymph node score). The SMOTE synthesis method was used to address the problem of minority sample imbalance; in patients affected by lymph node PCR. In the random forest machine-learning model, the AUC was 0.85. For statistical analysis or the nomogram method, they used univariate logistic regression to study the correlation of clinicopathological and echographic features with lymph node PCR and to retain in the nomogram only those features significantly in multivariate logistic regression. The effectiveness of multiparametric MRI in the pretreatment prediction of breast tumors resistant to NAC was assessed by Xiong, Q [53]. On clinical data as well as radiomics parameters such as morphological, textural, and wavelet characteristics extracted from MRIs of 125 patients, they used the logistic regression model. An AUC of 0.986 was obtained in the primary cohort using the combined prediction model based on radiomic and clinical parameters, while an AUC of 0.935 was achieved in the validation dataset.

Braman [55] assessed the efficacy of radiomic textural analysis of intratumoral and peritumoral areas on pretreatment contrast-enhanced dynamic MRI of breast cancer (DCE-MRI) to predict PCR following neoadjuvant chemotherapy (NAC) in this research. They extracted 99 radiomic textural features from the DCE-MRIs, then used five models including LDA (linear discriminant analysis), DLDA (diagonal linear discriminant analysis), QDA (Quadratic discriminant analysis), Naïve Bayes and SVM and trained them on these features after selection to predict PCR. The DLDA model performed best for data from hormone receptor-positive and human epidermal growth factor receptor 2-negative patients (HR+, HER2 -) with an AUC of 0.83 and with an AUC of 0.72 before separating the data according to receptor subtypes. They found from their results that the radiomic features most predictive of response varied according to different receptor subtypes. Thus, they found that intra- and peri-tumoral features of DCE-MRI could be useful in predicting pretreatment PCR.

Other studies

Some other categories of studies focused on classical methods like radiomic or imaging methods with or without machine learning. The majority of other research focused on an important topic in breast cancer research: obtaining a radiomic biomarker for PCR following neoadjuvant chemotherapy. In [55], they discovered that DCE-MRI intra- and peri-tumoral characteristics could help in the pretreatment prediction of PCR. In [72], they found that the apparent diffusion coefficient of the breast tumor on MRI is a biomarker of PCR in women undergoing neoadjuvant chemotherapy. In [73], Kurtosis, one of the texture analysis characteristics is an interesting biomarker for the identification of triple-negative BC because it seems to be linked to PCR to neoadjuvant chemotherapy in non-triple-negative breast cancer. In [74], the textural characteristics DOS (Diffuse Optical Spectroscopy) performed before treatment can predict breast cancer response to NAC and possibly guide therapies.

Performance evaluation of ML and DL approaches

While we have distinct datasets, various imaging modalities, and different parameters and circumstances for each work to the others, it is impossible to compare the machine learning and deep learning techniques. If we say that it is only feasible to compare works in the same category, in the deep learning technique, for instance, we have models that have utilized data with Multiple Treatment Time Points and various data kinds. Thus, we are unable to compare the performance of the works. Table 2 shows us, despite the different data used, that certain works [35, 40, 42] perform better than others [37–39] when using data with several treatment time points. As a result, data with multiple treatment time points and multiple kinds can improve prediction.

The challenges of implementing AI in medicine

On one hand, there are many hurdles to getting AI in medicine up and running. Some of the major challenges in adoption and implementation of AI in healthcare are as follows [72]:

1. *Data Accessibility and Quality:* For training, AI models require large, diverse, and labeled datasets (labeled training data), as most models do not understand how to process incomplete, outlier and high tolerance data. However, more than likely, you have a hard time grandfathering and handling the raw data because healthcare data is so often broken, for example. In addition, the data is scattered around different systems and lost. Concerns for data security and pri-

vacy adds more complexity to sharing and incorporating healthcare data.

2. *Ethical and legal considerations*: AI in medicine introduces very complex ethical scenarios. It is important to explicitly and thoughtfully address the key issues associated with AI deployment, such as privacy, informed consent, bias, transparency and accountability. This is needed as it ensures AI algorithms are unbiased, equitable, and provides transparency for patient safety and confidence. Legal Framework—Implementation of laws to regulate AI use in healthcare.
3. *Generalizability:* The ability of the AI model to generalize to new demographics, geographies, patient groups etc., if it was trained on a certain dataset or healthcare context. Differences in healthcare data collection, demographics or practices can affect how effectively or quickly AI models can deliver benefits in different contexts.
4. *Successful integration into clinical workflows:* The value of AI applications in healthcare is rooted in the ability of these technologies to integrate seamlessly into existing workflows. More often, though, what is required is the transformation of both the infrastructure, instructions, and user interface in order to assimilate the AI tools deep into clinical practice. Integration challenges may arise due to resistance to change, limited resources, lack of system interoperability, or limited clinical buy-in.
5. *Explainability and Interpretability:* deep learning models in general are known as "black boxes", meaning it is hard to know how they reach to a decision. In the healthcare domain, you can win the trust of the professionals only when the system is interpretable, a business will ensure transparency and provide treatment recommendations with explanations only if the model is interpretable. One hot research area right now is developing AI methods that are intuitively explainable for the health care industry
6. *Validation and Regulatory Compliance* is crucial to guaranteeing safety, effectiveness, and dependability for AI in healthcare. Before models can be applied clinically, exacting validation research and adherence to regulation are demanded to prove accurate and consistent functioning. Standardizing assessment frameworks and guidance for AI in medicine remains an ongoing undertaking.
7. *Acceptance and education of clinicians is key to the adoption of AI.* Doctors may be concerned about the impact on their work, decision-making autonomy and doctor-patient relationships. To encourage acceptance and promote effective collaboration, sufficient training and communication of the pros and cons are essential. However, complex systems also raise difficult questions about accountability and oversight; progress will depend on building understanding and partnership between disciplines.

Limitations of previous works

Table 4 shows the most general and common limitations between previous works. For the data limitation problem, almost all works used small datasets from a single institution; for the human intervention problem, some works, like [35], required manual data preprocessing for tumor volume cropping; in [36], tumor-containing slices were selected manually; and in [47], feature extraction was done manually. For the generalization problem, all works required validation by datasets from different institutions.

Then, to overcome these problems, our future studies will try to propose predictive models, which will specify a personalized treatment for each patient according to their pathological situation, and try to generalize them, i.e., apply models that have already been trained on an institution-specific dataset to other datasets from different institutions.

The limitation of our work is that we did not perform a meta-analysis of the literature as most of the research used private data, making it difficult to access data and codes. Although we emailed the authors to request access to the code and data, we regrettably got no answer.

Conclusion and future work

In order to account for the increasing variety of machine learning (ML) and deep learning (DL) algorithms, the main objective of this research study is to identify highly effective algorithms for monitoring and predicting responses to neoadjuvant therapy in breast cancer patients. An exhaustive review of how artificial intelligence (AI) methodologies have been applied to solve the problem is employed. This study provided an overview of the most recent research in the field of medicine, particularly in the area of personalized oncology, which includes breast cancer, as well as the most recent methods, including AI-based methods. Table 2 and 3, gives an overview of some of the works in the literature and their performances allowing us to remark that the most used models, which gave good performances in machine learning; SVM, XGBoost, and LR, while in deep learning, most of the works focused only on the CNN or pre-trained CNN model. To overcome the limitations of the works listed in Table 4, we

Table 4 Limits of previous works

Study	Limited dataset	Human intervention	Generalization problem
Hongyi Dammu [34]	x	No	Yes
Syed A [46]	x	No	Yes
Mohammed El Adoui [35]	x	Yes	Yes
Benjamin Q. Huynh [36]	x	Yes	Yes
Peng [37]	x	Yes	Yes
Richard Ha [38]	x	Yes	Yes
Amirhessam Tahmassebi [47]	x	Yes	Yes
Elizabeth Hope Cain [48]	x	Yes	Yes
Sunghoon Joo [39]		No	Yes
Maria Colomba [40]	x	No	Yes
Ke ZR [49]	x	No	Yes
Aghaei F [50]	x	No	Yes
Li, F [42]		Yes	Yes
Xie J [42]	x	Yes	Yes
Meng Jiang [43]		Yes	Yes
Zhou T [51]	x	Yes	Yes
Bao Li [44]	x	No	Yes
Hongyi Duanmu [45]	x	Yes	Yes
DiCenzo [52]	x	Yes	Yes
Xiong, Q [53]	x	Yes	Yes
Kotaro Yoshida [54]	x	Yes	Yes
Braman [55]	x	Yes	Yes

can use several techniques even if there is limited data, such as Federated Learning, and Few-Shot Learning in future research. Since there are data from different treatment moments that have sequential data, we try to apply or combine CNN with one of the existing sequential models.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13049-0.

Supplementary Material 1.

Authors' contributions

Methodology, Writing—original draft, R.H; Writing—review & editing, R.H.; review, S.A; Supervision, A.Y., J.R.,H.T., M. El. and M.B. All authors reviewed the manuscript.

Funding

No funding.

Data availability

The data used and/or analyzed in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 21 June 2024 Accepted: 8 October 2024
Published online: 21 October 2024

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