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REVIEW ARTICLE

A REVIEW OF AI-BASED RADIOMICS AND COMPUTATIONAL PATHOLOGY APPROACHES IN TRIPLE-NEGATIVE BREAST CANCER: CURRENT APPLICATIONS AND PERSPECTIVES

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ABSTRACT

Breast cancer is among the most prevalent and lethal tumors globally. Approximately 20% of all breast cancers are classified as triple-negative (TNBC). Triple-negative breast cancer (TNBC) is generally linked to a worse prognosis compared to other breast cancer subtypes. Conventional cytotoxic chemotherapy is the standard treatment due to its aggressiveness and resistance to hormone therapy; nevertheless, this approach is not consistently effective, and a significant proportion of patients experience recurrence. Recently, immunotherapy has been employed in certain populations with TNBC, demonstrating encouraging outcomes. Regrettably, immunotherapy is applicable to only a small subset of patients, and the responses in metastatic triple-negative breast cancer have been rather moderate compared to other cancer types. This situation demonstrates the necessity for the development of effective biomarkers to stratify and personalize patient care.Recent advancements in artificial intelligence (AI) have generated heightened interest in its application for medical purposes, particularly in enhancing clinical decision-making. Numerous studies have employed AI with diagnostic medical imaging, particularly in radiog-

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INTRODUCTION

Aside from skin cancer, breast cancer is the most prevalent cancer among women, accounting for almost 10% of all new cancer cases worldwide. It ranks as the fifth principal cause of cancer mortality globally, responsible for over 700,000 fatalities. In 2022, an estimated 300,000 additional cases were anticipated to be detected among women in the United States. Breast cancer is categorized into various subtypes based on, among other factors, a molecular profile determined by the differential expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor. When a breast carcinoma is devoid of all these receptors, it is termed triple-negative breast cancer (TNBC). Triple-negative breast cancer (TNBC) constitutes approximately 20% of all breast cancer cases and, in contrast to other variants, exhibits more rapid growth and dissemination, a poorer prognosis, and limited therapeutic alternatives owing to its unresponsiveness to hormone therapy and targeted HER2 agents. Recurrences in TNBC patients are thoroughly documented, with a comprehensive examination of cases revealing an increased likelihood of distant metastases and mortality within five years after diagnosis. Seven Furthermore, patients with TNBC exhibit a greater mortality rate relative to other subtypes, with a median time to death of approximately 4 years, in contrast to 6 years for non-TNBC patients. The treatment of patients with triple-negative breast cancer (TNBC) poses a difficulty due to its aggressiveness and unresponsiveness to hormone therapy. Eight Genomic assays like Oncotype DX (21 genes) and Mammaprint (70 genes) assist in the therapy of some breast cancer types, such as hormone receptor-positive and HER2-negative cancers; however, they are not advised for triple-negative breast cancer (Wilkinson et al., 2022; Bianchini et al., 2016).

Due to the absence of identifiable targetable biomarkers, standard cytotoxic chemotherapy has been the predominant treatment for patients with triple-negative breast cancer (TNBC) in both early and advanced stages of the illness. Interestingly, people with triple-negative breast cancer (TNBC) exhibit a superior response to chemotherapy compared to those with other breast cancer subtypes; however, this treatment is not

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universally beneficial, particularly for those with metastatic TNBC, who are destined to succumb to the disease. In recent years, there has been an increasing focus on the development of new multidrug combination systemic medicines in the neoadjuvant and adjuvant contexts to enhance current treatment outcomes. Nonetheless, several studies are contentious because to the associated toxicities (e.g., platinum drugs), while others are in preliminary stages and necessitate further validation in independent patient cohorts. Although chemotherapy has been the conventional treatment for triple-negative breast cancer (TNBC), significant progress in cancer immunotherapy, particularly with immune checkpoint inhibitors (ICI), has transformed treatment approaches for advanced cancer during the past decade. Recent clinical trials have demonstrated encouraging pathologic complete response (pCR) rates of up to 90% for patients with triple-negative breast cancer (TNBC) receiving immune checkpoint inhibitors (ICI). Regrettably, the efficacy of immunotherapy in metastatic triple-negative breast cancer has been limited relative to other malignancies and is relevant to only a small subset of patients. Patient selection is essential to identify individuals with TNBC who will benefit from specific therapy, allowing those unlikely to react to avoid related toxicities and be steered toward alternative treatments (Wu et al., 2021).

Another significant concern regarding TNBC is that various researches indicate this disease disproportionately impacts Black (African American) women. Although the prevalence of breast cancer is lower among Black women compared to White women, the disease-specific death rate is twice as high in Black women. Black women with TNBC exhibited a 21% elevated mortality risk compared to White women, even after controlling for treatment-related variables. Likewise, they exhibited a reduced pCR to neoadjuvant chemotherapy (NACT) in comparison to White women, suggesting that Black patients may possess more resistance to chemotherapy (Dietze et al., 2015). A potential explanation for this may be unequal access to health and social resources; nevertheless, another credible cause is the existence of morphological and molecular variations in the illness phenotype. A study by Hoskin et al. indicated that tissue-based genomic assays, such as OncotypeDx, may exhibit reduced accuracy in underserved communities, particularly among Black women. This raises the question of how to integrate these population-specific characteristics in the development of new companion diagnostic tools for monitoring treatment regimens for TNBC patients (Chen et al., 2023).

The challenging circumstances of TNBC have highlighted the necessity for the development of appropriate predictive and prognostic biomarkers to enhance patient stratification and management personalization. Traditionally, physicians have utilized radiological scans and histopathological tissue samples to diagnose and direct the treatment of patients with TNBC; however, these images and samples contain disease-specific information that may not be readily discernible to the human eye and, consequently, may remain underutilized. Due to enhancements in computer capacity and the emergence of novel approaches, there is a growing interest in the application of artificial intelligence (AI) for medical purposes to assist clinical decision-making (Sukumar et al., 2021).

In recent years, artificial intelligence and deep learning have been integrated with medical imaging, leading to the advancement of radiomics (derived from radiological scans) and computational pathology (based on histopathological samples). These methodologies employ computational tools to extract quantitative data and intricate patterns that are challenging for physicians to discern. The data obtained through these methods demonstrates significant potential for tasks such as risk stratification of patients to identify those with higher likelihood of illness recurrence or mortality, as well as predicting pathological complete response (pCR). This manuscript begins with a summary of AI, deep learning, radiomics, and computational pathology-based methodologies. Subsequently, we examine pertinent AI-driven prognostic and predictive biomarkers for TNBC utilizing radiomics and computational pathology methodologies. Finally, we examine the potentialities and challenges in the progression and clinical implementation of AI algorithms. This encompasses the differentiation of individuals who may derive benefit from targeted treatments such as chemotherapy or immunotherapy, directing them towards appropriate therapies while identifying those unlikely to benefit. Furthermore, we examine published research that investigates the possibility of revealing differences among populations and identifying unique subtypes of the disease (Hosny et al., 2018).

AI and Imaging Biomarkers

AI and Deep Learning

Artificial Intelligence is a domain of computer science wherein a computer is utilized to resolve intricate problems by mimicking the actions of an intelligent human in analogous circumstances.Due to advancements in AI and machine learning over the past decade, numerous "intelligent" models are significantly impacting daily life and have revolutionized various industries through their enhanced performance and efficiency in predictive tasks. Two prevalent methodologies exist for deriving feature representations in the development of AI models.The initial method is sometimes referred to as handcrafted feature extraction, which employs existing domain knowledge to discern features that may be advantageous for the computer in addressing a problem. The second is commonly referred to as unsupervised feature learning, enabling the computer to autonomously discern the pertinent properties for problem-solving (Ray et al., 2022).

A prominent instance of this unsupervised feature learning methodology is deep learning, a category of machine learning techniques that endeavors to learn through examples utilizing artificial neural networks (abstract representations of human neural architecture) with numerous layers. A deep-learning system autonomously identifies representations that differentiate between relevant categories within a data set. Convolutional neural networks (CNN) are a specialized type of artificial neural networks designed for image processing.Recent improvements in processing capabilities and resources have significantly enhanced the recognition of CNNs, demonstrating their efficacy in addressing many computer vision problems, including picture categorization, segmentation, and object detection. Notable CNN architectures encompass LeNet5, AlexNet, VGG, InceptionNet, ResNet, and U-Net. Generative adversarial networks (GAN) comprise two concurrently trained neural networks: the generator and the discriminator. The generator is designed to produce counterfeit images to deceive the discriminator, while the discriminator strives to differentiate

between authentic and artificially generated images. Generative Adversarial Networks (GANs) have proven beneficial for applications including style transfer and object segmentation (Manakitsa et al., 2024).

AI-Based Imaging Biomarkers in TNBC

Machine Learning Based Prognostication in TNBC

Various studies have employed diverse viewpoints in the development of imaging-based prognostic biomarkers that utilize visual data from radiological or histological images to identify individuals at elevated risk of illness recurrence or mortality.

Biomarkers Derived from Computational Pathology. The progression of cancer is a multifaceted process dependent on the interactions of tumor cells, the microenvironment, and the immune system, which can either facilitate or inhibit tumor growth and invasion. This has prompted the pursuit of biomarkers that indicate the immunological status and forecast the probability of therapeutic response. Tumor-infiltrating lymphocytes (TILs) consist of various immune cell types, including cytotoxic T cells, natural killer cells, dendritic cells, helper T cells, B cells, and regulatory T cells. They are regarded as indicators of the adaptive immune response and may signify immune-mediated host defense against tumors. Notably, elevated levels of tumor-infiltrating lymphocytes (TILs) are typically found in triple-negative breast cancer (TNBC) and HER2-positive breast cancer relative to hormone receptor-positive (HR-positive) breast cancers. Clinical trials and retrospective analyses indicate that tumor-infiltrating lymphocytes (TILs) function as synergistic agents, correlating with enhanced disease-free and overall survival in triple-negative breast cancer (TNBC) patients undergoing adjuvant anthracycline-based chemotherapy, pembrolizumab, or other neoadjuvant therapies (Zhou et al., 2024).

The evaluation of lymphocytic infiltration is presently conducted through visual inspection, supported by recommendations to assist pathologists in achieving proper quantification; yet, this method is labor-intensive, expensive, subjective, and susceptible to errors. Consequently, various investigations have employed computational technologies to achieve an objective quantification of tumor-infiltrating lymphocytes (TILs) in histopathological samples from patients with triple-negative breast cancer (TNBC). In these studies, authors have gathered samples stained with H&E and/or IHC (e.g., CD3, CD4, CD8, CD20, or FOXP3) and have utilized automated segmentation to delineate tissue compartments (e.g., tumor and stroma) while identifying TILs and other cellular entities through either proprietary machine learning models (deep neural networks) or AI-driven software applications (e.g., QuPath, Visiopharm, or HALO).Subsequently, they extracted many quantitative metrics linked to TILs, including the overall count of TILs, the number of stromal TILs, the ratio of TILs to tumor cells, and the abundance of CD8-positive cells, among others. Consistent with prior research, these results indicate that a high density of tumor-infiltrating lymphocytes (TILs) correlates with enhanced survival, highlighting the potential of computational techniques for automated quantification (Nearchou et al., 2019).

Tumors and their microenvironments are spatially organized ecosystems consisting of various cell types that can exhibit diverse phenotypes characterized by the coexpression of multiple proteins. This indicates that the study of tumor biology and treatment responses should incorporate spatial information. Certain researches have endeavored to surpass density metrics by conducting a spatial characterization of tumor-infiltrating lymphocytes in triple-negative breast cancer. For instance, Mi et al. utilized automated methods on IHC samples to delineate cellular clusters within tissue regions (invasive front, central tumor, and normal tissue) and subsequently collected morphometric features from these clusters. The invasive front exhibits elevated densities of immune cells, underscoring its significance in the tumor immunological architecture. Yuan39 employed an automated image analysis method to identify and categorize cells in H&E samples (Smith et al., 2019). A quantitative assessment of the intra-tumor lymphocyte ratio was subsequently calculated based on the distances between tumor-infiltrating lymphocytes and individual cancer cells, as well as clusters of cancer cells.This metric was substantially correlated with disease-specific survival in TNBC. Likewise, the deep learning to construct TIL maps from H&E samples of patients with TNBC and other breast cancer variants. They derived TIL spatial features from these maps and calculated a TIL score, which correlated with patient outcomes. Ultimately, it is established that TNBC patients with residual invasive illness exhibit a worse prognosis than ER-positive patients with residual invasive disease. In a preliminary investigation developed an AI-based model that delineates the spatial architecture of tumor-infiltrating lymphocytes (TILs) in residual triple-negative breast cancer (TNBC) following neoadjuvant chemotherapy (NACT) with H&E data. This model constructs clusters of TILs and non-TILs, extracting attributes from these clusters to identify patients at elevated risk of mortality and recurrence. While these studies emphasize the significance of examining the spatial architecture of tumors rather than individual cells, a notable limitation is the relatively small sample sizes utilized. Further investigation is necessary to ascertain whether these methods can generalize to real-world situations (Corredor et al., 2019).

Most studies have employed AI to identify TILs and other nucleated cells, subsequently extracting information such as density or spatial distribution. Conversely, some have adopted an unsupervised feature learning methodology, wherein the system autonomously learns and selects relevant features from the image while optimizing class separability. For instance the deep learning algorithm that takes immunofluorescence images of CD8+ T cells as input and predicts whether a patient with TNBC is likely to have a favorable or unfavorable result (Abousamra et al, 2022). Handcrafted methods, such as those deriving metrics from TILs, are generally straightforward to understand since each feature can be examined independently; conversely, deep learning models are frequently termed "black boxes" due to their interpretative complexity. Consequently, authors employing deep learning methodologies are urged to utilize procedures that facilitate a more profound comprehension of the rationale behind specific predictions. Grad-CAM is a method that emphasizes areas of an input image that are most pertinent to the model's judgment, allowing users to understand the model rationale (Vandoni et al., 2019).

Biomarkers Derived from Computational Pathology. Various AI-based imaging predictors for pCR have been documented in

the literature, with the majority employing deep learning methodologies. Study developed a deep learning algorithm to predict responses to neoadjuvant chemotherapy using pre-treatment samples. This model attained a moderate area under the receiver operating characteristic curve (AUC) of 0.65 in predicting pathological complete response (pCR) using a dataset of H&E-stained samples from patients with triple-negative breast cancer (TNBC) scanned at 40x magnification (Li et al., 2021). Three deep learning models were employed for tumor bed detection and nuclear feature analysis, followed by the extraction of characteristics pertaining to nuclear color, shape, and texture. The aforementioned variables were employed to train a logistic regression model aimed at predicting response to neoadjuvant chemotherapy (NACT), resulting in an accuracy of 79% for both partial and complete responses. A significant weakness of this study, however, is the limited sample size. Experiments utilizing pre-treatment samples from 73 individuals with triple-negative breast cancer (TNBC) achieved 93% accuracy at the patient level. Recent study introduced a federated learning methodology, utilizing 519 entire slide images from patients at two cancer hospitals to employ several neural networks for predicting pCR. This method attained AUCs of 61.5 and 78 on a validation subset for the first and second centers, respectively. This study reveals that machine learning models utilizing entire slide images may predict responses to neoadjuvant chemotherapy, and that collaborative training enhances their performance (Zakareya et al., 2023).

Challenges and Opportunities

Novel and Underexplored Biomarkers

The majority of contemporary AI-driven imaging prognostic biomarkers have concentrated on the analysis of tumor-infiltrating lymphocytes (TILs). Nonetheless, as previously noted, a significant body of research has focused on identifying mutations and subtypes of TNBC linked to prognosis and treatment response, hence offering a substantial possibility for the development of innovative AI-imaging biomarkers. Previous study indicates that the downregulation of PI3K may be crucial in identifying glioblastoma patients likely to react to immune checkpoint inhibitors (ICI). Considering this, many investigations devised a radiomics methodology in a preliminary study that extracted features pertaining to form, intensity, fractal characteristics, and texture from MRI for the automated diagnosis of PI3K-activated glioblastoma. A similar strategy might be formulated for TNBC, wherein the PIK3CA gene represents one of the most prevalent mutations, therefore aiding in the identification of patients who might benefit from immunomodulation. Shiri et al. created a radiomics signature utilizing PET/CT imaging to predict KRAS and EGFR mutations in non-small cell lung cancer, which were linked to responses to targeted therapy. This methodology might be applied to the TNBC domain to uncover imaging characteristics associated with responses to PARP inhibitors or androgen receptor modulation, for instance. Similarly, additional prospective biomarkers identifiable through image analysis encompass cytokine signaling pathways linked to immunomodulators; HR signaling related to LAR; growth factor signaling pathways pertinent to the mesenchymal subtype; and the downregulation of immune response, cell activation, and DNA repair pathways associated with BLIS. AI for Identifying Potential Differences between Populations

As previously stated, TNBC disproportionately impacts certain communities, such as Black women. Computerized analysis of photos from patients with TNBC facilitates the examination of tissue morphology and architecture, potentially revealing biological variations among various populations. Many studies have demonstrated that morphological differences between Black and White populations are statistically significant in oropharyngeal cancer. AI has the ability to deliver more optimal and customized disease outcome forecasts for TNBC, which may assist underprivileged areas and be pivotal in efforts to eradicate inequities.

Statements and Declarations

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Availability of data and materials

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