Current Status and Advances in Imaging Evaluation of Neoadjuvant Chemotherapy of Breast Cancer

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Abstract: It is particularly important to evaluate the efficacy of neoadjuvant chemotherapy (NAC) for breast cancer. This article reviews the current status and progress of imaging evaluations regarding the efficacy of NAC in women with breast cancer, including mammography, ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET-CT) and radiomics. Each imaging method has value for evaluating the efficacy of NAC for breast cancer, but certain defects and limitations. Therefore, the optimal selection will employ a combination of multiple imaging methods that will not only benefit patients but also avoid the unnecessary waste of medical resources.

Key words: Neoadjuvant therapy; Breast neoplasms; Mammography; Ultrasonography; Computed tomography; MRI; PET-CT

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Breast cancer is one of the most common malignant tumors among women, and its incidence is increasing annually. For example, the incidence rate of breast cancer increased by 0.3% per year in the US over the last 5 years (2012-2016), largely because of rising rates of local stage and hormone receptor-positive disease. Therefore, it is of great importance to find efficient and precise treatments of local-stage breast cancer with different molecular subtypes [1, 2]. Neoadjuvant chemotherapy (NAC) for breast cancer is primarily used to treat locally advanced breast cancer before surgery and is indicated for patients with breast cancer in clinical stages II and III. NAC not only downstages the tumor, which helps to increase the choice of surgical methods, but also tests the response of chemotherapy in advance, while serving as an important research tool to screen for efficacy predictive molecules and pharmacokinetic parameters. In addition, it can directly verify the drug efficacy through repeated biopsy [3]. A recent meta-analysis conducted by the US Food and Drug Administration reviewed work that included 12 international centers and enrolled 11,955 patients.

The results confirmed that the survival rate of those who achieved complete pathological remission after receiving NAC was significantly improved [4]. Therefore, evaluating the efficacy of NAC is particularly important. Although pathology is the gold standard evaluation, it is invasive, slow, and difficult to perform during chemotherapy [5, 6]. Clinical palpation is simple, but it is highly subjective and relies solely on palpable size of the mass. As a noninvasive and reproducible examination method, imaging has value when evaluating the efficacy of NAC. Numerous studies have reported that different imaging methods, including mammography, ultrasound (US), computed tomography (CT), nuclear magnetic resonance imaging (MRI), positron emission tomography (PET-CT) and radiomics, have beneficial clinical value for the evaluation of NAC efficacy. However, no standard examination method is recognized for the efficacy evaluation of NAC in clinical practice. This article reviews the current status and progress of imaging evaluations regarding the efficacy of NAC for women with breast cancer.

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Mammography

Mammography has been widely used in clinical practice given its advantages of simple operation, and affordability. It clearly shows the microcalcifications of breast cancer [7] and can be used to evaluate NAC efficacy by comparing the changes in breast mass characteristics, such as size, shape, and calcification (Fig. 1) as well as the changes in perilesional and axillary lymph nodes before and after NAC. Chagpar et al. [8] retrospectively analyzed the data of 189 patients and found that mammography was significantly superior to clinical palpation; however, its measured post-NAC residual lesion size was only moderately correlated with the pathologically measured size after surgery (correlation coefficient $r = 0.41$), and the diagnostic accuracy was only 70%. Liu et al. [9] reported that the change rate of mass was 89.3%; of these changes, 87.5% of round masses showed irregular changes, the edges of 93.7% of fuzzy masses became clear, the burr of 90.5% of masses with peripheral burr became shorter or even disappear, and 74.2% of lesion calcifications changed in range, number, and distribution. Thus, mammography was expected to be used to evaluate the efficacy of NAC. However, mammographic assessment on the efficacy of NAC has limitations. For example, its accuracy is dependent on whether the mass boundary is clearly visualized before treatment. Huber et al. [10] found that the accuracy of assessing the rate of masses changing after treatment was highly correlated to masses with clear boundaries before treatment ($r = 0.77$), whereas the correlation was low for masses with unclear boundaries ($r = -0.19$). In addition, lesion calcifications can increase, decrease, or remain unchanged after NAC [11], making it difficult to evaluate efficacy. Moreover, mammography irradiates the human body, it is not accurate enough to detect multicentric breast cancer, and it does not differentiate well between tumor residue after chemotherapy and chemotherapy-induced fibrosis [12]. Therefore, its application value for evaluating the efficacy of NAC in breast cancer is worth exploration but requires further refinement.

Ultrasound

Routine ultrasonography

Routine ultrasonography is primarily used to observe changes in the location, number, size, morphology, boundary, internal echo, and posterior echo of breast mass. Keune et al. [13] studied 192 patients with breast cancer treated with NAC and found that ultrasound detected 91.3% of all cases with tumor remnants after chemotherapy, whereas X-ray only detected 51.9% of all cases. Thus, the authors argued that ultrasound was more accurate than X-ray while measuring the size of the

residual tumor after chemotherapy (Fig. 1). Roubidoux MA [14] used ultrasound to measure the maximum diameter of the mass before and after NAC to calculate the reduction rate (%) of tumor diameter and compared that value with the histopathological efficacy of NAC. The author found that ultrasound had a higher sensitivity while evaluating the efficacy of NAC for breast cancer by measuring the change in the size of the mass and reflected the efficacy of NAC more accurately; moreover, other studies [15] have supported this view. Many reports have previously documented the assessment of NAC efficacy via color Doppler by observing the changes in blood flow signal, maximum blood flow velocity (Vmax), and the resistance index (RI); however, recent studies have shown that the accuracy of its measurement is low, and the application value is not high. However, the ability of conventional ultrasound to predict pathological complete remission after NAC does not significantly

Figure 1 A 29-year-old woman with a left breast lesion which was confirmed as invasive breast cancer. After completion of neoadjuvant chemotherapy, Transverse ultrasound (A and B) showed a heterogeneous hypoechoic lesion (arrows) without blood flow signal, likely reflecting residual tumor. Mammography (C and D) and CT examination (E and F) showed microcalcifications (arrows) correlating with ultrasound findings. Pathological examination after surgery confirmed residual tumor.

differ from that of X-ray, and the accuracy of both is approximately 80% [13]. Studies have shown that the predictive power of the combined application of the two is better than that of any single measurement [16]. Although conventional ultrasound has some value when evaluating the efficacy of NAC, its demonstration of calcification is not as effective as mammography, and it cannot differentiate residual tumors after chemotherapy from chemotherapy-induced fibrosis [17].

Contrast-enhanced ultrasound (CEUS)

CEUS is able to demonstrate the distribution process of contrast agents in tumor blood vessels (especially tumor microvessels) in real time and dynamically through the intravenous injection of ultrasound contrast agents that can reflect the distribution of, survival of, and changes to tumor microvessels [18, 19]. Numerous recent publications have reported that CEUS qualitatively and quantitatively assesses the changes in tumor blood perfusion after NAC in patients with breast cancer. After NAC, the use of CEUS imaging to measure the size of residual tumor is more accurate than conventional ultrasound, especially in areas where the center of the tumor has undergone apoptosis without liquefaction necrosis. Furthermore, CEUS better shows areas without enhancement that cannot be identified using conventional ultrasound [20–22]. The sensitivity, specificity, positive predictive value, and negative predictive value of CEUS in predicting the complete remission of cases following NAC have reached as high as 80%, 98%, 88.9%, and 96%, respectively [23]. Compared with two-dimensional CEUS, three-dimensional CEUS (3D-CEUS) more accurately reflects the changes in the internal perfusion of the tumor and tumor blood vessels before and after NAC in women with breast cancer. Chen Man [24] used 3D-CEUS to evaluate the efficacy of NAC in women with breast cancer. Compared with pre-NAC, the 3D-CEUS score after NAC was significantly decreased. The sensitivity of using the 3D-CEUS score to evaluate the efficacy of NAC in women with breast cancer was 100.0%. However, this method is expensive, has currently not been validated in appropriately sized multicenter trials, and has not been widely used in the clinical evaluation of NAC efficacy.

Ultrasound elastography

Ultrasound elastography can further evaluate the degree of softness/hardness of objects based on conventional ultrasound that includes the following technologies (Fig. 2). (1) Acoustic radiation force impulse (ARFI) imaging technology is used to evaluate NAC efficacy with regard to breast cancer by measuring the softness/hardness of the internal and marginal

tissues of tumors, including the virtual touch tissue image (VTI) technique and the virtual touch tissue quantification (VTQ) technique. (2) Real-time shear wave elastography is used to reflect NAC efficacy with regard to breast cancer by measuring the absolute value of Young's modulus, a value that reflects tissue elasticity. Greater values of Young's modulus denote higher elastic coefficients (i.e., harder objects). Hayashi [25] found that breast cancers with low elastographic measurement values (i.e., softer tumors) had significantly higher pathological complete remission rates after NAC than those with high measurement values (i.e., harder tumors), indicating that elastography has value for NAC efficacy prediction. Evans et al. [26] found a significant correlation between the shear wave elastography measurement values before NAC treatment and the complete remission rate of cases after treatment in cases of non-progressive breast cancer. Han et al. [27] found that the elastographic measurement values of tumors with effective treatment were significantly reduced after 2 courses of NAC treatment, but no such difference was found in the group with ineffective treatment. However, many factors affect the accuracy of breast ultrasound elastography, such as the depth and size of the lesion and the background of the perilesional tissue, whereas the size and depth of the lesions usually change after NAC treatment, which limits its application when evaluating the efficacy of NAC.

Ultrasonic spectrum analysis

The ultrasonic spectrum analysis seeks to extract relevant tissue information using the radio-frequency (RF) echo signal to perform a fast Fourier transform and a spectrum analysis. Ultrasound RF signals include single-frame RF signals and RF time-series signals, and numerous previous studies have confirmed that RF signals contain detailed information related to the tissue microstructure. Therefore, RF signal analysis can be used to observe the changes in microstructure of tumor tissue before and after chemotherapy [28, 29]. Tran et al. [28] found that the data from a single-frame RF signal analysis showed significant difference one week after NAC in patients with breast cancer, indicating that it can be used for efficacy evaluation. Sadeghi-Naini et al. [28] found that using the changing rate of RF single-frame signal analysis data better distinguished chemotherapy responsive tumors from chemotherapy refractory tumors after four weeks of NAC treatment with a 100% sensitivity and an 83.3% specificity. Ultrasound RF time-series signals are better able to assess tissue microstructure than single-frame RF signals, but their evaluation of chemotherapy efficacy in patients with breast cancer remains in the experimental stage. Clearly,

ultrasound RF signal analysis is an emerging technique, and its application value for NAC evaluation in patients with breast cancer must be further explore.

CT scan

At present, CT scanning has evolved into multi-slice spiral CT scanning. The images obtained from this method have the characteristics of wide range, high spatial resolution, and high contrast resolution; moreover, they can be used to reconstruct coronal and sagittal multiplanar images, which have certain application values for evaluating the efficacy of NAC in patients with breast cancer (Fig. 1). CT can be used with high accuracy (up to 88%) morphological assessment, including lesion

size [31]. Xu Min et al. [32] compared the range of residual lesions assessed using multi-slice spiral CT with the range confirmed by the histopathological diagnosis of breast cancer after NAC treatment and found that the consistency rate was as high as 90.9%. Unenhanced CT accurately reflects the changes in breast cancer lesions and lymph nodes before and after NAC, and enhanced CT reflects vascularity of breast cancers before and after NAC treatment. Although CT has value while evaluating the efficacy of NAC in patients with breast cancer, it also has deficiencies. For example, CT has a lower display rate of microcalcification in breast cancer lesions than mammography does, and patients must receive more radiation during the examination, which somewhat limits its clinical application.

Figure 2 A 44-year-old women with a left breast lesion which was confirmed as invasive breast cancer. Before neoadjuvant chemotherapy, a solid, hypoechoic lesion with well-defined margin was detected with conventional ultrasound (A). The elasticity imaging (EI, B) and the virtual touch tissue imaging (VTI, C) reflected tissue elasticity was hard. In virtual touch tissue quantification (VTIQ), the highest shear wave velocity was 5.27 m/s (D). After two weeks of neoadjuvant chemotherapy, the lesion size decreased and the margin became ill-defined (E). The EI and VTI reflected tissue elasticity was still hard (F and G), while in VTIQ, the highest shear wave velocity decreased to 3.84 m/s (H).

MRI

MRI not only accurately measures the size and morphology of tumors but also provides information on the blood supply, physiological, and biochemical metabolic information within the tumor. These methods include dynamic contrast-enhanced MRI (CE-MRI), diffusion-weighted MRI (DWI-MRI), hydrogen proton magnetic resonance spectroscopy, and magnetic resonance perfusion imaging, which can be used to more accurately evaluate the efficacy of NAC in patients with breast cancer. At present, however, more studies have

focused on CE-MRI and DWI-MRI (Fig. 3).

Dynamic CE-MRI

CE-MRI can be used to detect angiogenesis during tumor progression and evaluate therapeutic efficacy by observing changes in microcirculation during tumor treatments. CE-MRI has been widely used in the literature to detect residual breast cancer following NAC. A meta-analysis that summarized 44 studies conducted between 1990 and 2008 with a total enrollment of 2,050 cases showed that CE-MRI had a higher sensitivity (sensitivity 83%-87%) for the detection of residual

lesions after NAC, although significant variation was found among studies with different specificities (specificity 54%-83%) [33]. Cho et al. [34] found that a voxel-based parametric response map analysis of DCE-MRI better predicted treatment-responsive tumors after the first course of NAC among patients with breast cancer. CE-MRI texture analysis is a quantitative assessment method for tumor heterogeneity, and a texture analysis based on enhanced and T2-weighted sequences may have better clinical prospects regarding the evaluation of NAC to treat breast cancer. Specifically, a small sample of 35 patients with locally advanced breast cancer was conducted by Wu et al. [35], who found that the rapid regression of areas of significant

heterogeneity in tumors predicted the effectiveness of chemotherapy. Another study that included 61 patients with breast cancer treated with NAC showed that if the tumor heterogeneity changed on T2-weighted sequences during treatment using a T2-weighted sequence-based texture analysis, then it was more closely correlated with treatment effectiveness, and this correlation was more pronounced among patients with triple-negative breast cancer [36]. However, DCE-MRI may also underestimate residual tumor after chemotherapy, possibly because chemotherapy drugs have an anti-angiogenic effect, and the decrease of blood vessels and the increase of fibrous tissue components after chemotherapy weakens tumor enhancement or changes the enhancement pattern [37].

Figure 3 A 57-year-old woman with multiple right breast lesions that underwent percutaneous biopsy, revealing invasive breast cancer. Before neoadjuvant chemotherapy, CE-MRI (A and B) showed area of clumped enhancement (arrows) with regional distribution, and DWI-MRI (C) showed heterogeneous masses (arrows) of right breast. After completion of neoadjuvant chemotherapy, CE-MRI (D and E) showed no residual enhancement, and DWI-MRI (F) showed no mass of right breast. Pathological examination after surgery confirmed complete pathologic response

Diffusion-weighted MRI

DWI-MRI is an imaging modality that measures the movement of water molecules. DWI-MRI images are quantitatively analyzed by determining the apparent diffusion coefficient (ADC) of water molecules within tissue. After effective chemotherapy, tumor cells die, resulting in a decreased cell density and increasing extracellular space. Thus, ADC values increase with effective NAC [38]. Based on these principles, DWI-

MRI can be used for the early assessment or prediction of NAC efficacy in patients with breast cancer. One study of 53 patients with breast cancer showed that after receiving NAC, the ADC value of the chemotherapy-responsive group was significantly lower than that of the chemotherapy-refractory group [39]. Another meta-analysis that summarized the literature documenting 34 studies indicated that sensitivities of DWI-MRI and CE-MRI were 93% and 68% respectively, and specificities

were 82% and 91% respectively, suggesting that the diagnostic efficacy of DWI-MRI was partially better than that of CE-MRI [40]. However, DWI-MRI also has limitations. At present, the greatest controversy in this area is the selection of the region of interest (ROI) for measurement. The position, size, and depth of the ROI significantly affect the accuracy and repeatability of the ADC measurement values. In addition, because the detection of tumor response to chemotherapeutic agents requires dynamic tracking and repeated examinations, which may be difficult due to the cost of MRI examination and longer examination time. Furthermore, contrast agents that can cause allergic reactions must be injected during the examination. Thus, these deficiencies have somewhat limited its widespread adoption in clinical practice.

Positron emission tomography (PET-CT)

¹⁸F-FDG PET imaging is a functional imaging technique that can be used for the study and detection of the biological changes in tumors under physiological conditions that do not affect the homeostasis of the internal environment of the human body. Tumors that respond to chemotherapy undergo significant changes in their metabolism before their volume is altered. As such, PET-CT has value when evaluating the NAC efficacy with regard to breast cancer. PET-CT has been widely used for the clinical diagnosis and treatment of breast cancer [41]. PET-CT can be used to track tumor treatment response as well as to timely or even quantitatively evaluate tumor metabolism, proliferation, drug resistance, and receptor status with which we can observe the early subclinical response of tumors to treatment and evaluate the short- and long-term efficacies after treatment to provide a basis for developing individual chemotherapy regimens and assessing prognosis. One study of 40 patients with invasive ductal carcinoma showed that PET-CT predicted the final chemotherapy efficacy because the relative changing rate of the standardized uptake value (SUV) of the tumors, which eventually achieved pathological complete remission after patients underwent two courses of NAC, was significantly higher than that of the tumors that eventually failed to achieve pathological complete remission [42]. A meta-analysis that summarized 19 papers including a total of 920 patients indicated that the diagnostic efficacy of PET-CT for the early evaluation of chemotherapy efficacy in women with breast cancer was not high; moreover, its sensitivity, specificity, positive predictive value, and negative predictive value were 84%, 66%, 50%, and 91%, respectively [43]. The biggest factor that contributed to these results was the

low spatial resolution of PET-CT for superficial masses. The literature reports that the sensitivity, specificity, and accuracy of PET-CT regarding the diagnosis of breast cancer lesions with diameters ranging from 3.1 to 8.0 mm are 93.3%, 90.9%, and 100%, respectively [43]. However, its diagnostic efficacy for masses less than 1 cm is significantly reduced and shows a high false negative rate. In addition, the cost of PET-CT is high, the radioactive contrast agent must be injected, and the examination process is also radioactive, which all limit its repeated use during the efficacy evaluation.

Radiomics

Radiomics is a newly-evolved field of medical imaging analysis, meaning conversions of digital medical images into mineable high-dimensional data, including both semantic and agnostic features. As is known, solid tumors are highly heterogeneous at the phenotypic, physiologic, and genomic levels, which is regarded as the main reason for resistance to tumor treatment. Radiomics enables quantitative measurement of intratumoral and intertumoral heterogeneity and reveals the relationships between information in biomedical images and the underlying pathophysiology; and the subsequent mining of these data helps to develop models for diagnosis, prediction, or prognosis [45, 46]. Radiomics has made progresses on prediction of NAC efficacy. A retrospective study with 60 patients for training and 186 patients for validation, in which each tumor was divided into multiple spatially segregated and phenotypically consistent sub-regions on the basis of perfusion MR imaging parameters, showed that perfusion MRI radiomics predicted the recurrence-free survival (RFS) after NAC because aggressive tumors were associated with a larger volume of the poorly perfused sub-region [47]. Besides analysis of the heterogeneity within tumors, radiomics can also provide us with that of regions around tumors. Braman et al. [48] conducted radiomic textural analysis of intratumoral and peritumoral regions on pretreatment DCE-MRI and found that radiomic features strongly predicted pathological complete response (pCR) after NAC independent of choice of classifier. Equipped with artificial intelligence, radiomics makes prediction easier. Drukker et al. [49] reported that the automatically-calculated most enhancing tumor volume by MRI radiomics could predict RFS in NAC of breast cancer at early treatment, of which performance rivaled that of combining a traditional semi-manual model, functional tumor volume (FTV), and knowledge of the pre-surgical residual cancer burden. Moreover, combining radiomic features with genomic data, so called radiogenomics, may increase diagnostic, prognostic, and predictive power. Ha et al. [50] divided 73 patients with locally

advanced breast cancer into different clusters according to metabolic radiomics patterns and found distinctive characteristics among the clusters with regard to Ki67 expression, response to NAC, and risk of recurrence. In all, radiomics analysis epitomize the pursuit of precision medicine, which helps to provide personalized treatments with integration of quantitative information with clinical, histological, and genomic data. However, the power of radiomics depends on the size and quality of the database, requests standard acquisition and big data for reproducibility, while also risking overfitting. In the future efforts to establish standard, sharing data as well as avoiding redundant feature extractions are needed.

Conclusions

In summary, the early, correct, and objective evaluation of breast cancer response to NAC provides better options for the clinical selection of chemotherapy drugs to develop appropriate treatment regimen, which helps to reduce unnecessary drug use and decrease the toxic side effects of chemotherapy and improve the survival and quality of life of patients. Various imaging methods have application value but certain defects and limitations. Therefore, clinicians should choose appropriate imaging methods to evaluate and predict the efficacy of NAC based on actual patient conditions in clinical practice. The optimal selection as well as reasonable application and combination of multiple imaging methods will not only benefit patients but also avoid the unnecessary waste of medical resources.

Conflicts of Interest

The authors declare no conflict of interests.

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