Prospective Explore of Clinical-Pathological Shrinkage Modes After Neoadjuvant Therapy in Breast Cancer

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Abstract

**Purpose:** The aim was to explore the clinical-pathological shrinkage modes which oriented by breast conserving surgery (BCS) purpose after neoadjuvant therapy (NAT) using three-dimensional (3D) MRI and pathology reconstruction, in order to guide the individualized selection of BCS candidates and scope of resection after NAT.

**Methods:** From April 2014 to 2018, 104 breast cancer patients underwent operation after NAT were included in this prospective study. All patients underwent MRI examinations before and after NAT. Breast residual tumors were prepared with sub-serial section. The 3D MRI and pathology models were reconstructed with 3D-DOCTOR software. The association and correlation between 3D MRI and pathology models were assessed. The traditional shrinkage modes included the surgical pathology complete response, solitary lesions without surrounding lesions, multinodular lesions, solitary lesions with adjacent spotty lesions and diffuse lesions. Combined with the MD Anderson Cancer Center BCS indications after NAT and traditional shrinkage modes, we derived clinical-pathological shrinkage modes which oriented by BCS purpose: clinical pathological-concentric shrinkage modes (CP-CSM) and clinical pathological-non concentric shrinkage modes (CP-NCSM). The CP-CSM means the longest diameter of residual tumor was less than 50% and $\leq 2 \text{cm}$ in comparison with the primary tumor before NAT. Other shrinkage modes were classified as CP-NCSM. Univariate and multivariate logistic regression analysis was conducted to identify the independent predictive factors of clinical-pathological shrinkage modes. A nomogram was developed based on variables in the final model with $p<0.05$.

**Results:** Based on the gold standard of 3D pathology reconstruction model-measured shrinkage modes, the accuracy, sensitivity and specificity of 3D MRI reconstruction for predicting the traditional shrinkage modes were 84.6%, 61.9% and 90.4%, respectively (Kappa value=0.497). The accuracy, sensitivity and specificity of 3D MRI reconstruction in predicting clinical-pathological shrinkage modes were 93.3%, 97.0% and 86.5%, respectively (Kappa value=0.850). Multivariate analysis showed that primary tumor stage (OR=2.059, 95%CI: 1.187-3.574), mammographic malignant calcification (OR=3.424, 95%CI: 1.437-8.161), molecular subtypes (OR=0.530, 95%CI: 0.364-0.772) and nodal down-staging after NAT (OR=0.183, 95%CI: 0.067-0.497) were independent predictors of clinical-pathological shrinkage modes (all $p<0.05$). A nomogram was created based on these four predictors. The AUC value was 0.833 (95%CI: 0.710-0.922). The calibration curve showed a satisfactory fit between the predictive and actual observation. With a median follow-up time of 77 months, the recurrence/metastasis rate in the CP-CSM group was 7.1% and 29.4%, respectively ($p=0.002$). Patients with CP-CSM had a better overall survival and disease-free survival (all $p<0.05$).

**Conclusion:** The 3D MRI reconstruction after NAT could accurately predict the extent of residual tumor. Combining clinical, imaging, molecular subtypes and NAT efficacy, the nomogram of clinical-pathological shrinkage modes showed sufficient predicting accuracy. And it could help to guide the individualized selection of BCS candidates and scope of resection after NAT, thereby achieve the minimum and effective
treatment. However, the applicability of the nomogram still needs to be externally validated. Patients with CP-NCSM after NAT had a worse prognosis.

1. Introduction

Neoadjuvant therapy (NAT) is currently administered to patients with locally advanced breast cancers, to breast cancer of poor prognosis (triple-negative and HER2-positive tumors, or with nodal involvement and/or high proliferation rates), or to early-stage breast cancer having an indication of systemic therapy [1–2]. The use of effective chemotherapy as well as targeted therapies such as trastuzumab and pertuzumab for HER-2 positive (HER2+) disease in the neoadjuvant setting have led to an increase in the rate of breast pathologic complete response (pCR) after NAT ranging from 40~67% depending on the study population [1–4]. A major clinical benefit of NAT is downstaging of the tumor. As a result, inoperable tumors may become operable and patients with large tumors could receive breast conserving surgery (BCS) to facilitate better cosmetic outcomes [2, 5]. For patients achieved radiological complete response (rCR), a subset of patients with negative imaging following NAT might be safely treated with radiation alone without breast surgery in the future [6–7].

The meta-analysis of EBCTCG showed that patients allocated NAT had an increased frequency of BCS (65% with NAT vs 49% with adjuvant therapy). At the same time, the meta-analysis also showed that NAT was associated with more frequent local-regional recurrence (LRR) than was adjuvant therapy: the 15-year LRR was 21.4% for NAT vs 15.9% for adjuvant therapy [8]. This result highlights the importance of an accurate tumor extent assessment for patients undergoing BCS after NAT [9]. The frequency of BCS had increased after NAT, however, accurate tumor extent assessment was difficult and shrinkage modes can be heterogeneous, making surgery technically more difficult than without use of NAT [8]. For patients planned to receive BCS after NAT, tumor-involved margins increase the risk of LRR [10]. So, for these patients, it is crucial to accurately access the residual tumor extent in order to achieve tumor-free margins. At the same time, precise preoperative assessment of shrinkage modes after NAT is important for guiding surgical management of the patients. The traditional shrinkage modes of residual tumors after NAT had been discussed in several literatures, and were divided into five categories: surgical pCR, solitary lesion without surrounding lesions, multinodular lesions, solitary lesion with adjacent spotty lesions and diffuse lesions [11–15]. The meta-analysis of EBCTCG showed that for patients with multinodular lesions, there would be no increase in LRR if they received BCS successfully [8]. That is to say, the traditional shrinkage modes would not sufficient as an indication for BCS after NAT. So, in order to guide the individualized selection of BCS candidates and scope of resection after NAT, we derived and define the clinical-pathological shrinkage modes which orientated by BCS purpose: clinical pathological-concentric shrinkage modes (CP-CSM) and clinical pathological-non concentric shrinkage modes (CP-NCSM) [16–17].

In this study, we firstly constructed the MRI and pathological three-dimensional (3D) reconstruction model of residual tumor after NAT. Based on the gold standard of 3D pathology reconstruction model-measured tumor size, we assessed the correlation and association in measuring residual tumor extent between 3D
MRI and pathology reconstruction. Then we explored and definite the clinical-pathological shrinkage modes which oriented by BCS purpose after NAT. In addition, we analyzed the predictors of clinical-pathological shrinkage modes, and generated a nomogram in predicting the clinical-pathological shrinkage modes after NAT. We performed survival analysis of clinical-pathological shrinkage modes.

2. Patients And Methods

2.1 Patients

One hundred and four female patients who treated at Shandong Cancer Hospital Breast Cancer Center were enrolled in this prospective study between April 2014 to 2018. The study was approved by the Shandong Cancer Hospital Ethics Committee (No. SDTHEC20110324). Written informed consent was obtained from all patients before participation in the study, and all procedures were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration. Adult women were included in this study if they 1) had histologically confirmed invasive breast carcinoma; 2) were clinical staging $T_{1-4}N_{0-3}M_0$; 3) agreed to undergone NAT for the primary breast cancer. Patients were excluded according to the pre-established exclusion criteria if they had undergone therapy prior to NAT, concurrent cancer, bilateral breast cancer, or distant metastases.

2.2 Treatment

Each patient underwent MRI examination twice, that is, before core biopsy and within 3 weeks after the last cycle of NAT. The mean interval time between the preoperative MRI examination and final surgery was 3 days (range 1~5 days).

Before NAT, all patients received core biopsy of the breast tumor and fine-needle aspiration of the clinical/image positive/suspicious axillary nodes guided by ultrasound. Then we placed clap markers in tumor. Hormone receptor (HR) was defined as positive with more than one percent expression rate. HER-2 receptor was considered as positive with immune-histochemical staining of 3+, or fluorescence in situ hybridization that was amplified [16]. After these evaluations, molecular subtypes could be classified into Luminal A subtype, Luminal B HER2 negative (Luminal B HER2-) subtype, HER2+ and Tripe negative (TN) subtypes to precisely evaluate the biomarker effect.

According to the newest Breast Cancer National Comprehensive Cancer Network Guidelines and the St. Gallen international consensus, all patients received standard dose four cycles of anthracycline and cyclophosphamide followed by four cycles of paclitaxel before surgery. HER2+ patients received anti-HER-2 targeted therapy.

After NAT, all patients underwent a series of evaluation by a multidisciplinary team to recommend for breast surgery. BCS or mastectomy were performed according to the multidisciplinary evaluation and patients’ preferences.
2.3 Magnetic resonance images (MRI) acquisition and 3D MRI reconstruction

MRI was performed using 3.0T scanners (Philips Medical Systems, Best, The Netherlands) with a dedicated 7 elements sense breast coil. Patients underwent imaging in the prone position with breast immobilized. The contrast material was intravenously using a bolus injection at a dose of 0.1mmol/kg followed by a 20 ml saline solution flush. The largest diameter of the tumor was measured at the initial enhancement series (90 seconds after contrast injection). The breast MRI imaging of all patients were independently assessed by two radiologists with experience in reading breast MRI. They were unaware of the pathological outcomes and used the same measurement standard to measure the tumor size. In cases of rim enhancement, the necrotic core was included in measurement of the largest diameter. In cases of multifocal or diffuse tumor growth, the complete enhancing area, including intermediate (non-enhancing) tissue around the tumor, was measured on maximum intensity projection images.

After scanning of the whole breast, bidimensional MRI images were transferred to 3D-DOCTOR software workstation to create and analysis 3D image of the breast. After delineating the extent of residual tumors in each MRI image, we chosen the command “3D Rendering/Surface Rendering/Simple surface”, then the 3D MRI model could be reconstructed (Figure 1) [17]. The shape and location of tumors in the breast and their relation to the adjacent tissues were examined. Using 3D images of MRI reconstruction model, the tumor size can be measured in the 3D planes, including transversal, sagittal and coronal planes (or at any other angle). When there was no discernible contrast enhancement or a faint enhancement equal to the background normal tissue in previous tumor bed, this case was determined as rCR on MRI [18].

2.4 Sub-serial sections of breast specimens and 3D pathology reconstruction

After mastectomy, according to the blue dye labeled extent of primary tumors, breast tissue specimens were excised with a distance of 3.0 cm from the tumor boundary. After BCS, entire excised specimens were prepared for sub-serial sections [19]. The upper margins of isolated specimens were marked with black ink, double-needle dyeing method to mark anchor points. Then the specimens were stored in a -20°C refrigerator. After drawing markers on the transversal plane, the specimen was cut into several blocks at 5.0-mm intervals based on the markers (Figure 2a). The tissue blocks were marked with continuous numbers and were immersed in 10% formalin solution for 48h. After performing routine procedures for dehydration and paraffin-embedded histology, we made one section of 4.0~6.0-µm thick in each block. The sections were cut using a Leica RM2010 slicer (Leica Biosystems, Nussloch, Germany) and stained with hematoxylin and eosin [16].

Finally, we used these sections to reconstruct sub-serial 3D pathology model. Invasive tumors, calcification and ductal carcinoma in situ (DCIS) were delineated and recorded under microscope respectively (Figure 2b). The sections’ images were collected with the Epson V600 scanner (resolution
360 bpi) and stored as JPG format. The JPG data were integrated and calibrated based on anchor points using Photoshop software. Then JPG data of each section was imported into the 3D-DOCTOR software. With the “3D Rendering/Surface Rendering/Simple surface” command, the sub-serial 3D pathology reconstruction model of residual tumor after NAT was presented (Figure 3). The residual invasive tumor, calcification and DCIS were marked with different colors in the 3D pathology reconstruction model.

2.5 The measurement of residual tumor

The images obtained by MRI were in the “prone position”, while the data obtained by 3D pathology reconstruction were in the “supine position”. Since the breast changes depending on the body position, the shape of the breast tumor might not change between the “supine” and “prone” positions.

The longest diameter, maximum cross-sectional area and volume of residual tumors were measured respectively according to the 3D MRI and pathology reconstruction models. The longest diameter refers to the longest distance in the 3D planes of residual tumors. Using the 3D-DOCTOR software, we select the “Boundaries in All Planes” command to project all the outlined tumor boundaries into the same plane and measure the longest diameter and the longest vertical diameter of each plane. Then, the maximum cross-sectional area could be calculated (the longest diameter × the longest vertical diameter). The volume could be automatically calculated by selecting the “Tools/Calculate Volumes” command from the 3D-DOCTOR software.

After surgery, the histopathological diagnosis of residual tumors was interpreted by two experienced pathologists. Surgical pCR was defined as no residual invasive tumor or DCIS within all slices [20].

2.6 Shrinkage modes after NAT

The BCS indications after NAT of MD Anderson Cancer Center (MDACC) include: ypT<2 cm, no vascular lymphatic invasion, single-focal lesions, and negative margins [21]. Combined with the BCS indications of MDACC and several traditional shrinkage modes, we define the clinical-pathological shrinkage modes which oriented by BCS purpose: CP-CSM and CP-NCSM [16–17]. The CP-CSM means the longest diameter of residual tumor was less than 50% and ≤2cm in comparison with the primary tumor before NAT, including surgical pCR, solitary lesion without surrounding lesions, multinodular lesions and solitary lesion with adjacent spotty lesions. The shrinkage modes that the longest diameter of residual tumor was more than 50% and (or) >2cm in comparison with the primary tumor before NAT were classified as CP-NCSM, including solitary lesion without surrounding lesions, multinodular lesions, solitary lesion with adjacent spotty lesions and diffuse lesions (Figure 4).

The covariates were selected after a bibliographic review and at the researchers’ discretion. The main covariates were age (continuous, non-linear), primary tumor stage, clinical nodal stage, lymph nodes downstaging (yes or no), menopausal status, mammographic malignant calcification (yes or no), and molecular subtypes.
The primary objective of this work was to explore and define the clinical-pathological shrinkage modes which oriented by BCS purpose after NAT. The second objective was to assess the association and correlation in measuring residual tumor extent between 3D MRI and pathology reconstruction. At the same time, the second objectives also included analyzing the predictors of clinical-pathological shrinkage modes, and generated a nomogram in predicting the clinical-pathological shrinkage modes after NAT.

2.7 Statistical analysis

For diagnostic accuracy based on the measurement of residual tumor size, the gold standard was defined as the 3D pathology reconstruction model-measured tumor size. Spearman rank correlation test and Bland-Altman method were used to evaluate the correlation and consistency between 3D MRI and pathology reconstruction measurement of residual tumor.

The association of different clinicopathological variables with clinical-pathological shrinkage modes was analyzed. Pearson chi-square test or Fisher exact test was used to perform univariate analysis on categorical variables. Multivariable logistic regression analysis was conducted to identify the independent predictive factors of CP-CSM by using backward stepwise analysis.

A nomogram was developed based on variables in the final model with \( p < 0.05 \) using “rms” package for R. Calibration of the nomogram was carried out by internal validation using the bootstrap resampling approach and was displayed using a calibration curve. The discrimination of the model was evaluated using the area under the curve (AUC) value of the ROC curve. Statistical analyses were performed using SPSS Statistics 22.0 software (IBM Corporation, Armonk, NY, USA) and R version 3.3.3 software (The R Foundation for Statistical Computing, Austria, Vienna). A \( p < 0.05 \) was considered statistically significant.

3. Results

3.1 Patients’ characteristics

Between April 2014 to 2018, 104 patients received full course of NAT regimens followed by surgery in our Breast Cancer Center. The median age of these patients was 49 years old (rang 25 to 70 years). In terms of breast surgery approach selected, 78.8% (82/104) of patients underwent mastectomy, the other 21.2% (22/104) of patients received BCS. The clinical characteristics of the patients are summarized in Table 1.
### Table 1
The clinical characteristics of 104 patients

| Characteristic                      | No. | %   |
|-------------------------------------|-----|-----|
| Molecular subtypes                  |     |     |
| Luminal A subtype                   | 23  | 22.1|
| Luminal B HER-2 negative            | 21  | 20.2|
| HER-2 positive                      | 33  | 31.7|
| Triple negative                     | 27  | 26.0|
| Clinical nodal stage                |     |     |
| cN₀                                 | 18  | 17.3|
| cN₁                                 | 41  | 39.4|
| cN₂                                 | 32  | 30.8|
| cN₃                                 | 13  | 12.5|
| Clinical tumor stage                |     |     |
| cT₁                                 | 11  | 10.6|
| cT₂                                 | 68  | 65.4|
| cT₃                                 | 13  | 12.5|
| cT₄                                 | 12  | 11.5|
| Breast surgery                      |     |     |
| mastectomy                          | 78  | 78.8|
| breast conserving surgery           | 22  | 21.2|

### 3.2 Traditional shrinkage modes after NAT

The traditional shrinkage modes of residual tumor after NAT presented by 3D MRI and pathology reconstruction were 33, 27, 13, 26, 5 cases and 34, 16, 19, 25, 10 cases among surgical pCR, solitary lesion without surrounding lesions, multinodular lesions, solitary lesion with adjacent spotty lesions and diffuse lesions, respectively.

### 3.3 Clinical-pathological shrinkage modes after NAT

According to the definition of clinical-pathological shrinkage modes, the CP-CSM and CP-NCSM was observed in 67 and 37 patients by 3D MRI reconstruction, respectively. CP-CSM and CP-NCSM was
observed in 70 and 34 patients by 3D pathology reconstruction, respectively.

Among patients with CP-CSM, the surgical pCR, solitary lesions without surrounding lesions, multinodular lesions and solitary lesions with adjacent spotty lesions were observed in 33, 22, 8, 4 and 34, 13, 12, 11 patients by 3D MRI and pathology reconstruction, respectively. Among patients with CP-NCSM, the solitary lesions without surrounding lesions, multinodular lesions and solitary lesions with adjacent spotty lesions and diffuse lesions were observed in 5, 5, 22, 5 and 3, 7, 14, 10 patients by 3D MRI and pathology reconstruction, respectively (Table 2).

| Shrinkage modes                                      | 3D MRI reconstruction | 3D pathology reconstruction |
|------------------------------------------------------|------------------------|------------------------------|
| CP-CSM                                               |                        |                              |
| Surgical pCR                                         | 33 (31.7%)             | 34 (32.7%)                   |
| Solitary lesion without surrounding lesions          | 22 (21.2%)             | 13 (12.5%)                   |
| Multinodular lesions                                 | 8 (7.7%)               | 12 (11.5%)                   |
| Solitary lesion with adjacent spotty lesions         | 4 (3.8%)               | 11 (10.6%)                   |
| CP-NCSM                                              |                        |                              |
| Solitary lesion without surrounding lesions          | 5 (4.8%)               | 3 (2.9%)                     |
| Multinodular lesions                                 | 5 (4.8%)               | 7 (6.7%)                     |
| Solitary lesion with adjacent spotty lesions         | 22 (21.2%)             | 14 (13.5%)                   |
| Diffuse lesions                                      | 5 (4.8%)               | 10 (9.6%)                    |

CP-CSM: clinical pathological-concentric shrinkage modes, CP-NCSM: clinical pathological-non concentric shrinkage modes

3.4 The clinical-pathological shrinkage modes were suitable to guide the selection of BCS candidates

According to the traditional shrinkage modes, 50 (48.1%) cases in this study were suitable for BCS; while according to the clinical-pathological shrinkage modes, 70 (67.3%) cases were suitable for BCS ($p=0.007$, Table 3).
Table 3
Candidates of BCS according to the traditional shrinkage modes and the clinical-pathological shrinkage modes

| Shrinkage modes                              | Suitable for BCS | Not-suitable for BCS |
|----------------------------------------------|-------------------|----------------------|
| Traditional shrinkage modes                 | 50 (48.1%)        | 54 (51.9%)           |
| Clinical-pathological shrinkage modes        | 70 (67.3%)        | 34 (32.7%)           |

Among patients with multinodular lesions and solitary lesions with adjacent spotty lesions, there were 52.3% (23/44) of patients present with CP-CSM who were suitable for BCS. Among patients with solitary lesions without surrounding lesions, there were 18.8% (3/16) of patients present with CP-NCSM who were not suitable for BCS.

3.5 The association and correlation between 3D MRI and pathology reconstruction in measuring residual tumor extent

The accuracy, sensitivity, specificity, positive predictive value and negative predictive value of 3D MRI reconstruction in predicting traditional shrinkage modes were 84.6%, 61.9%, 90.4%, 61.9% and 90.4%, respectively (Kappa value=0.497, \( p<0.001 \)) (Table 4).

Table 4
The traditional shrinkage modes after NAT between 3D MRI and pathology reconstruction

| Traditional shrinkage modes | MRI    | Pathology | AC  | SE  | SP  | PPV | NPV  |
|-----------------------------|--------|-----------|-----|-----|-----|-----|------|
| Surgical pCR                | +      | 26  7     | 85.6| 76.5| 90.0| 78.8| 88.7 |
|                             | -      | 8  63     |     |     |     |     |      |
| Solitary lesion without surrounding lesions | +      | 8  19     | 74.0| 50.0| 78.4| 29.6| 89.6 |
|                             | -      | 8  69     |     |     |     |     |      |
| Multinodular lesions        | +      | 7  6      | 82.7| 36.8| 92.9| 53.8| 86.8 |
|                             | -      | 12  79    |     |     |     |     |      |
| Solitary lesion with adjacent spotty lesions | +      | 18  8     | 85.6| 72.0| 89.9| 69.2| 91.0 |
|                             | -      | 7  71     |     |     |     |     |      |
| Diffuse lesions             | +      | 5  0      | 95.2| 50.0| 100.0| 100.0| 94.9 |
|                             | -      | 5  94     |     |     |     |     |      |

AC=Accuracy; SE=Sensitivity; SP=Specificity; PPV=Positive predictive value; NPV=Negative predictive value
The 3D MRI and pathology reconstruction had a high consistency in assessing clinical-pathological shrinkage modes (Kappa value=0.850, \( p < 0.001 \)). The accuracy, sensitivity, specificity, positive predictive value and negative predictive value of 3D MRI reconstruction in assessing the clinical-pathological shrinkage modes were 93.3%, 97.0%, 86.5%, 92.9% and 94.1%, respectively (Table 5).

### Table 5

The clinical-pathological shrinkage modes after NAT between 3D MRI and pathology reconstruction

| Pathology  | MRI   | Total |
|------------|-------|-------|
|            | CP-CSM| CP-NCSM|     |
| CP-CSM     | 65    | 5     | 70  |
| CP-NCSM    | 2     | 32    | 34  |
| Total      | 67    | 37    | 104 |

CP-CSM: clinical pathological-concentric shrinkage modes, CP-NCSM: clinical pathological-non concentric shrinkage modes

For diagnostic accuracy based on the measurement of residual tumor size, the gold standard was defined as the 3D pathology reconstruction model-measured tumor size. The correlation among the longest diameter, maximum cross-sectional area and volume of residual tumors after NAT measured by 3D MRI and pathology reconstruction has statistically significance, respectively. And the \( r \) value was 0.942, 0.941 and 0.903, respectively (all \( p < 0.001 \)). Compared with 3D pathology reconstruction, 3D MRI reconstruction slightly underestimated the maximum diameter and maximum cross-sectional area of residual tumors, with a median disparity (\( MD \)) of -0.074cm (95% CI: -0.313~0.165cm) and -1.148cm\(^2\) (95% CI: -2.146~0.148 cm\(^2\)). And it overestimated the volume of residual tumors compared with 3D pathology reconstruction, with \( MD \) of 0.433 cm\(^3\) (95%CI: -9.55~12.34 cm\(^3\)).

### 3.6 The covariates associated with clinical-pathological shrinkage modes after NAT

Although there was no important difference in year and menopausal status among the clinical-pathological shrinkage modes after NAT, significant difference between clinical-pathological shrinkage modes and primary tumor stage before NAT (\( p=0.009 \)), clinical nodal stage after NAT (\( p=0.013 \)), lymph nodes downstaging after NAT (\( p<0.001 \)), mammographic malignant calcification (\( p=0.002 \)) and molecular subtypes (\( p<0.001 \)) were observed in univariate analysis. Variables with \( p \)-value<0.05 in the univariate analysis were assessed for multivariate analysis. The independent predictors of clinical-pathological shrinkage modes were comprised of primary tumor stage (OR=2.059, 95%CI: 1.187-3.574, \( p=0.001 \)), mammographic malignant calcification (OR=3.424, 95%CI: 1.437-8.161, \( p=0.005 \)), molecular subtypes (OR=0.530, 95%CI: 0.364-0.772, \( p=0.001 \)) and nodal down staging after NAT (OR=0.183, 95%CI: 0.067-0.497, \( p=0.010 \)) (Table 6).
Table 6
The predictive factors for clinical-pathological shrinkage modes after NAT

| Factors                        | CP-CSM | CP-NCSM | Univariable analysis | Multivariable analysis |
|-------------------------------|--------|---------|----------------------|------------------------|
|                               |        |         | p value              | p value                |
| Clinical tumor stage          |        |         | 0.009                | 0.001                  |
| cT1                           | 10     | 1       |                      |                        |
| cT2                           | 48     | 20      |                      |                        |
| cT3                           | 7      | 6       |                      |                        |
| cT4                           | 5      | 7       |                      |                        |
| Clinical nodal stage          |        |         | 0.659                |                        |
| cN0                           | 12     | 6       |                      |                        |
| cN1                           | 25     | 16      |                      |                        |
| cN2                           | 23     | 9       |                      |                        |
| cN3                           | 10     | 3       |                      |                        |
| Nodal stage after NAT         |        |         | 0.013                |                        |
| ycN0                          | 38     | 11      |                      |                        |
| ycN1                          | 17     | 7       |                      |                        |
| ycN2                          | 8      | 8       |                      |                        |
| ycN3                          | 7      | 8       |                      |                        |
| Molecular subtypes            |        |         | 0.001                | 0.001                  |
| Luminal A                     | 8      | 15      |                      |                        |
| Luminal B HER2-               | 14     | 7       |                      |                        |
| HER2+                         | 26     | 7       |                      |                        |
| TN                            | 22     | 5       |                      |                        |
| Lymph nodes downstaging       |        |         | 0.001                | 0.010                  |
| Yes                           | 61     | 20      |                      |                        |
| No                            | 9      | 14      |                      |                        |
| Malignant calcification       |        |         | 0.002                | 0.005                  |

CP-CSM: clinical pathological-concentric shrinkage modes, CP-NCSM: clinical pathological-non concentric shrinkage modes
| Factors | CP-CSM | CP-NCSM | Univariable analysis | Multivariable analysis |
|---------|--------|---------|----------------------|-----------------------|
|         |        |         | p value | p value | |
| Yes     | 29     | 23      |         |         | |
| No      | 41     | 11      |         |         | |

CP-CSM: clinical pathological-concentric shrinkage modes, CP-NCSM: clinical pathological-non concentric shrinkage modes

Based on data obtained from multivariate analysis, a nomogram was created to predict patients with CP-NCSM (Figure 5a). The model was developed based on the principles of transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD statement) [22]. To calculate the probability of CP-NCSM, the scores for the four factors were summed up. And the total scores and bottom risk scale were referenced. The overall performance and discriminative performance of the model were assessed by the calibration curve and ROC curve analysis, respectively. Based on internal validation with a bootstrap resampling frequency of 1000, the calibration curve showed a satisfactory fit between the predictive and actual observation (Figure 5b). The ROC curve of the nomogram was depicted in Fig. 5c. The AUC value was 0.833 (95%CI: 0.710-0.922, $p<0.001$), indicating that the nomogram had a good discriminatory capability.

### 3.7 Follow-up

The median follow-up was 77 months (40-134 months), with the last follow-up in August 2021. Seven cases were lost to follow-up (3 cases in CP-CSM subgroup and 4 cases in CP-NCSM group), and the effective follow-up rate was 93.3% (97/104). We observed 5 cases of recurrences/metastasis (7.1%) in the CP-CSM group and 10 cases (29.4%) in the CP-NCSM group ($p=0.002$). In CP-CSM group, one patient had chest wall recurrence and 4 patients had distant metastases. While in CP-NCSM group, 2 patient had chest wall recurrence, and 8 patients had distant metastasis. At the same time, the multivariate analysis also showed that clinical-pathological shrinkage mode was the independent predictors of recurrence/metastasis.

The median overall survival (OS) in CP-CSM and CP-NCSM group was 108.5 months and 89.0 months, respectively (Fig. 6a, $p=0.007$). The median disease-free survival (DFS) was 65.5 months and 60.5 months, respectively (Fig. 6b, $p=0.006$) in patients with CP-CSM and CP-NCSM. Patients with CP-CSM had a better survival compared to patients with CP-NCSM.

Previous studies had confirmed that pCR after NAT was associated with survival benefits. We want to exclude the effect of pCR on the survival benefit of CP-CSM group. So, we performed a subgroup analysis to assess survival benefit of patients who did not achieve pCR. The median OS in CP-CSM and CP-NCSM group was 102.0 months and 89.0 months, respectively (Fig. 6c, $p=0.024$). The median DFS was 101.5 months and 60.5 months, respectively (Fig. 6d, $p=0.025$) in patients with CP-CSM and CP-NCSM. Even
patients with CP-CSM did not achieve pCR, they also had a better survival benefit compared to patients with CP-NCSM.

4. Discussion

The continuous optimization of local-regional control under the guidance of molecular subtype allows clinicians to make reasonable adjustments based on the efficacy of NAT to achieve the maximum treatment benefits. For patients who plan to receive BCS after NAT, the 5-year LRR rate was 2~7% in patients with tumor-free margins, but the risk increased to as high as 22% if the margin was positive [7]. In EBCTCG meta-analysis involving 10 randomized controlled trials of NAT, more frequent LRR was associated with NAT compared with adjuvant chemotherapy (15-year risk of 21.4% for NAT vs. 15.9% for adjuvant therapy) after BCS [8]. For patients who received BCS after NAT, in cases of multifocal residual tumor and/or cases of scattered residual tumor, the 2017 St. Gallen consensus conference expressed an opinion to favor more “generous” margins [23]. However, the 2019 St. Gallen consensus conference recommended that the optimal resection remains removal of all known residual as opposed to original tumor lesions with a margin goal of “no ink on tumor” regardless of the presence of unifocal or multifocal disease [24]. Three strategies to mitigate the increased LRR after BCS in tumors downsized by NAT should be considered: careful tumor localization (including place marker clip, tumor range, and shrinkage modes), detailed pathological assessment, and appropriate radiotherapy [8]. After NAT, tumor extent assessment can be difficult and shrinkage modes can be heterogeneous, making surgery technically more difficult than without use of NAT. So, for patients who plan to receive BCS after NAT, it is important to accurately assess residual tumor extent and shrinkage modes after NAT to ensure negative margins and reduce LRR as well as resection rate.

In this study, we constructed the 3D MRI and pathology model of residual tumor after NAT. Based on the gold standard of 3D pathology reconstruction model-measured tumor size, we found that the 3D MRI reconstruction after NAT could accurately predict the extent of residual tumor. At the same time, we explored and define the clinical-pathological shrinkage modes which oriented by BCS purpose after NAT. In addition, a nomogram was developed based on the predictors of clinical-pathological shrinkage modes that might aid clinicians in surgical decisions. The nomogram indicated that patients with large primary tumor, mammographic malignant calcification, Luminal A/Luminal B HER2- subtype, and high nodal burden after NAT were more likely to present with CP-NCSM. With an AUC of 0.833 and internal validation using the bootstrap resampling method, the model exhibited sufficient ability to predict clinical-pathological shrinkage modes after NAT.

The main strength of the study was that we constructed the BCS-oriented clinical-pathological shrinkage modes which combined shrinkage modes with residual tumor extent. Compared with traditional shrinkage modes, clinical-pathological shrinkage modes were suitable to guide the individualized selection of BCS candidates and scope of resection. This mode could help to decrease the negative margins distance and simultaneously maintain the natural breast shape to facilitate better cosmetic outcomes. And it represents a transformation of treatment concept, which from maximum and tolerable
treatment to the minimum and effective treatment. The traditional view believed that multinodular lesions and solitary lesion with adjacent spotty lesions were not suitable for BCS. However, in our study, for patients with a high probability of CP-CSM after NAT, even if they had multinodular lesion or solitary lesion with adjacent spotty lesion, BCS would also be safe if they had a negative margin. And for these patients, there would be no increase in LRR if they received BCS successfully. For patients with a high probability of CP-NCSM, the basic goal of NAT (tumor downstage) had not been achieved. If satellite lesions were missed during surgery, LRR would increase due to “false negative margins”. So, these patients need to be cautious when choosing BCS, at the same time, they also need a more “generous” resection extent. The 2019 St. Gallen consensus conference also recommended that patients with multi-focal disease could also accept BCS after NAT, but the scope of residual tumors need to be more accurately assessed. Therefore, our study might partly expand the indications of BCS: patients might also accept BCS safely even if they had multi-focal disease after NAT.

MRI has an increased sensitivity, accuracy and specificity in detecting residual disease in the breast compared to either mammogram or ultrasound, making it a potentially useful tool in neoadjuvant setting [25–26]. Over the past several years, the correlation between MRI and pathology in assessing residual tumors extent in breast cancer patients receiving NAT has been the topic of several publications [14, 25–32]. The meta-analysis of 35 clinical trials confirmed that the correlation of residual tumors size assessed by MRI and pathology varied from poor to excellent (range 0.210–0.982) [26]. The 3D MRI provides an intuitive image of tumor extent in the breast and is helpful for surgeons to plan surgery. Furthermore, it can display more precise information than routine bidimensional images, because 3D tumor images can be observed from various directions by rotation [9, 33–37]. Taking advantage of these characteristics, 3D MRI has a high degree of accuracy in assessing the residual tumor extent after NAT. Although several reports have demonstrated that 3D MRI significantly and strongly correlated with pathology examination [31–32, 38], most of these researches compared the tumor extent which was assessed by its largest diameter at 3D MRI model with the pathology examination of routine sliced images.

The 3D pathology reconstruction has been previously used in researches, and it could also provide more precise information about tumor extent than routine sliced images [16–17, 11, 19, 39]. Wang S et al. [11] reconstructed 3D pathology models and analyzed the correlation with clinical pathological factors. Kazuaki et al. [39] just reconstructed 3D models of whole breast. Zheng et al. [19] analyzed the association between 3D pathology reconstruction and mutant-allele tumor heterogeneity value. However, as far as we know, most of these studies did not compare the association and correlation between 3D MRI reconstruction and 3D pathology reconstruction in evaluation of residual tumor extent. In this study, taking 3D pathology reconstruction-measured tumor size as the gold standard, we further confirmed the accuracy of 3D MRI reconstruction in assessing residual tumor extent after NAT. At the same time, the MRI images were easy to obtain, and the 3D reconstruction technology was relatively mature. So, we recommend applying 3D MRI reconstruction techniques to evaluate residual tumor extent after NAT in clinical practice.
In this study, the correlation value was 0.942 among the longest diameter measured by 3D MRI and pathology reconstruction. In addition, the correlation about maximum cross-section and volume of residual tumors after NAT were also highly correlated. However, MRI may underestimate or overestimate residual disease compared with pathology examination [40]. In this study, 3D MRI reconstruction had a slight underestimation of the maximum diameter and cross-section compared with 3D pathology reconstruction. Reasons might be that the anti-vascular effects of chemotherapy resulted in lack of inflammatory reactions surrounding the tumor [41]. On the other hand, 3D MRI reconstruction overestimated the maximum volume of residual tumor, reasons might be that the changes in cellularity or vascularity of tumors after NAT did not reflect in the change of overall tumor volume. Although tumor cells were destroyed, the tumor fibrosis remained. Some drastic pathologic changes induced by chemotherapy, such as tumor degeneration, severe fibrosis, inflammatory reactions and surrounding necrosis [37], could result in non-specific contrast enhancement in the tumor bed, which might be mistaken as residual tumors by MRI.

The study of Ippei et al. [12] showed that traditional shrinkage modes were significant associated with tumor size and number of metastatic lymph nodes (all \( p<0.05 \)). Our research group performed a series of studies, the results showed that patients with lower mutant-allele tumor heterogeneity value and lower primary tumor/nodal burden were more likely to present with CP-CSM after NAT (all \( p<0.05 \)) [16, 19]. Xu et al. [42] confirmed that TN and HER2+ subtypes had more chance to achieve CP-CSM compared with Luminal A and Luminal B HER2- subtypes, \( (p=0.042) \). Katsuhiro et al. [43] reported that the concentric shrinkage pattern may be more commonly found in TN subtype than in other molecular subtypes. Our results also showed that molecular subtype was an independent predictor of the clinical-pathological shrinkage modes. The correlation between molecular subtype and clinical-pathological shrinkage modes might reflect tumor biologic characteristics. One possible reason might be the growth characteristic of Luminal A and Luminal B HER2- subtypes, tumor cells tend to grow slowly with low apoptosis rate and genetic instability [12]. Simultaneously, tumor cells in these subtypes may be more resistant to preoperative therapy. However, tumor cells in TN and HER2+ subtypes had poor differentiation and strong proliferation ability, the aggressive tumor cells were more sensitive to therapy [44]. After NAT, the tumor boundary of patients with CP-CSM was easy to judge, and the margins of these tumors were often negative after finishing tumor resection. But the tumor boundary of patients with CP-NCSM is difficult to determine accurately. For those patients, LRR might be increased due to “false negative margin” when performing BCS. Therefore, Luminal A and Luminal B HER2- patients with large primary tumor and/or high nodal burden after NAT should be cautious to receive BCS after NAT, and the negative margin distance might also need to be appropriately increased. Although some patients with TN and HER2+ subtypes had the poor prognosis, patients with these subtypes were more likely to present with CP-CSM after NAT, suggesting that BCS after NAT was also feasible for TN and HER2+ patients.

Shrinkage modes were reported to be associated with prognosis. Ippei et al. [12] found patients with concentric shrinkage pattern has an excellent DFS \( (p=0.007) \) and OS \( (p=0.037) \). Our study also found that the clinical-pathological shrinkage modes were related to the survival. Patients with CP-CSM also had a
better DFS and OS. The reasons might be that the predictors associated with CP-CSM indicated lower tumor burden, and these predictors were associated with a better prognosis.

This study has certain limitations, and the most important of which is the small sample size. Additionally, in this study, the follow-up time is relatively short. So, long-term follow-up is still needed to verify our study. Thirdly, lacking multi-center external data to verify the accuracy of the nomogram is another limitation in our study. Since our study has small sample size, so we performed internal cross-validation with a bootstrap resampling frequency of 1000. We will further increase the number of cases and divide them into training and validation set in the future. Therefore, further prospective multi-center studies are required to confirm and assess the results of this study.

5. Conclusion

The 3D MRI and pathology reconstruction have a good association and correlation in the evaluation of clinical-pathological shrinkage modes after NAT. The 3D MRI reconstruction after NAT could accurately predict the extent of residual tumor. Combining clinical, imaging, molecular subtypes and NAT efficacy, a nomogram of clinical-pathological shrinkage modes showed sufficient predicting accuracy. And it could help to guide the individualized selection of BCS candidates and scope of resection after NAT, thereby achieve the minimum and effective treatment. However, the applicability of the nomogram still needs to be externally validated. Patients with CP-NCSM after NAT had a worse survival.

Declarations

Ethics approval and consent to participate: Written informed consent was obtained from all patients before participation in the study. The study protocol was approved by independent ethics committees at every participating center, and the study was undertaken in full accordance with the Declaration of Helsinki.

Consent for publication: All authors agreed to publish this article.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors have stated that they have no conflicts of interest in this work.

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Wang YS and Zhao T have approved the final completed version of this paper and assume accountability for all aspects of the work.

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Figures
Figure 1

The 3D MRI reconstruction model of residual tumor after NAT.

Figure 2

a. The tissue was cut into several blocks and marked with continuous numbers. b. The extent of residual tumors was delineated under microscope.
Figure 3

The 3D pathology reconstruction model of residual tumor after NAT. The red marks represent invasive tumors, green marks mean ductal carcinoma in situ, and purple marks represent calcification.
Figure 4

The clinical-pathological shrinkage modes of residual tumors after NAT. The CP-CSM means the longest diameter of residual tumor was less than 50% and ≤2cm in comparison with the primary tumor before NAT, including surgical pCR, solitary lesion without surrounding lesions, multinodular lesions and solitary lesion with adjacent spotty lesions. The shrinkage modes that the longest diameter of residual tumor was more than 50% and (or) >2cm in comparison with the primary tumor before NAT were classified as CP-NCSM, including solitary lesion without surrounding lesions, multinodular lesions, solitary lesion with adjacent spotty lesions and diffuse lesions.
A nomogram to predict CP-NCSM after NAT. The overall performance and discriminative performance of the nomogram were assessed by the calibration curve and ROC curve analysis, respectively. 

a: To calculate the probability of CP-NCSM, the scores for the four factors were summed up. And the total scores and bottom risk scale were referenced.

b: The calibration curve showed a satisfactory fit between the predictive and actual observation.

c: The ROC curve of the nomogram.
Figure 6

The survival analysis between CP-CSM and CP-NCSM group. a: The OS in CP-CSM and CP-NCSM group. b: The DFS in CP-CSM and CP-NCSM group. c: The OS in CP-CSM and CP-NCSM group of patients who did not achieve pCR. d: The DFS in CP-CSM and CP-NCSM group of patients who did not achieve pCR.