

# Feasibility of quantitative and volumetric enhancement measurement to assess tumor response in patients with breast cancer after early neoadjuvant chemotherapy

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## Abstract

**Objective:** To evaluate the feasibility of quantitative enhancing lesion volume (ELV) for evaluating the responsiveness of breast cancer patients to early neoadjuvant chemotherapy (NAC) using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

**Methods:** Seventy-five women with breast cancer underwent DCE-MRI before and after NAC. Lesions were assessed by ELV, response evaluation criteria in solid tumors 1.1 (RECIST 1.1), and total lesion volume (TLV). The diagnostic and pathological predictive performances of the methods were compared and color maps were compared with pathological results.

**Results:** ELV identified 29%, 67%, and 4% of cases with partial response, stable disease, and progressive disease, respectively. There was no significant difference in evaluation performances among the methods. The sensitivity, specificity, positive predictive value, negative predictive value (NPV), and accuracy of ELV for predicting pathologic response were 72%, 92%, 81.8%, 86.8%, and 85.3%, respectively, with the highest sensitivity, NPV, and accuracy of the three methods. The area under the receiver operating characteristic curve was also highest for ELV. Pre- and post-NAC color maps reflecting tumor activity were consistent with pathological necrosis.

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**Conclusions:** ELV may help evaluate the responsiveness of breast cancer patients to NAC, and may provide a good tumor-response indicator through the ability to indicate tumor viability.

### Keywords

Breast cancer, dynamic contrast-enhanced magnetic resonance imaging, enhancing lesion volume, RECIST 1.1, neoadjuvant chemotherapy, pathologic response, total lesion volume

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## Introduction

Breast cancer is the most common cancer in women worldwide and often has a poor prognosis.<sup>1</sup> Descriptive epidemiological studies of breast cancer in China<sup>2</sup> have shown that the number of breast cancer patients recorded in Chinese urban cancer registries has increased by 20% to 30% in the past 30 years, with an annual growth rate of 3% to 5%.<sup>3,4</sup>

Neoadjuvant chemotherapy (NAC) is currently a standard treatment for patients with breast cancer in stage II or III. Previous studies showed that NAC provided an effective treatment for breast cancer by reducing tumor size and metastasis and recurrence rates, and thus improving the likelihood of pathological complete response and the long-term prognosis.<sup>5,6</sup> Unlike conventional adjuvant chemotherapy, NAC allows earlier treatment of micro-metastases.<sup>7</sup> Accurate and timely assessment of tumor response and residual tumor tissue after NAC is thus crucial in clinical settings.<sup>8</sup>

Magnetic resonance imaging (MRI) is considered as the reference standard imaging modality for breast cancer evaluation and has demonstrated better diagnostic accuracy than other conventional imaging methods (mammography and breast ultrasonography) and clinical breast examination.<sup>9–13</sup> Importantly, MRI provided a

better correlation between disease progression and pathological response when used to monitor disease progression during treatment, compared with clinical evaluation and conventional imaging.<sup>14–22</sup> Dynamic contrast-enhanced MRI (DCE-MRI) is currently used to evaluate the response of NAC to breast cancer. It may allow the early identification of responders and non-responders and may predict the presence of residual tumor after early NAC.<sup>22–24</sup> Some reports indicated that DCE-MRI could indicate the tumor pathophysiological response to NAC before any changes in tumor volume.<sup>25–28</sup>

The response evaluation criteria in solid tumors (RECIST) criteria are commonly used to assess solid tumor response, and the updated RECIST 1.1 criteria also consider the associated pathological lymph nodes.<sup>29</sup> However, although RECIST 1.1 is widely used to evaluate breast tumors,<sup>30,31</sup> it has some limitations, such as in lesions with complex shapes, irregular margins, and/or a complex growth pattern, which are difficult to assess using dimensional criteria. Dimensional measurements also have some limitations in the presence of fibrosis or necrotic tissue. In particular, the persistence of nonviable residual masses after treatment leads to an underestimation of the response based on dimensional criteria.<sup>32</sup>

Breast cancer is a heterogeneous and vascular-dependent tumor, the internal anatomical structure of which changes constantly, especially after chemotherapy. Anatomical measurements may thus only reflect part of the changes. In addition, anatomy-based methods often fail to show treatment-induced changes in intratumoral viability in response to NAC. Anatomical imaging may be limited in its ability to distinguish between viable residual tumor tissue and reactive changes, such as scar tissue and edema.<sup>33</sup>

The current study aimed to assess the feasibility of applying an enhancement-based method, enhancing lesion volume (ELV), for assessing the therapeutic response after early NAC in patients with breast cancer on DCE-MRI images, compared with the current anatomy-based methods, RECIST 1.1 and total lesion volume (TLV).

## Methods

### *Patient selection and data collection*

This retrospective study was approved by the ethics committee and Institutional Review Board of the People's Hospital of Ningxia Hui Autonomous Region (Institutional Review Board No. 2020-KY-116). Studies were conducted in accordance with national law and the Declaration of Helsinki 1964 (and subsequent revisions). Informed consent was obtained from all participants in the study. Patients at our hospital with suspected breast cancer diagnosed by ultrasound from January 2012 to July 2019 were included. Patients diagnosed with benign breast nodules by core needle biopsy or mammography were excluded. Patients who received surgery without NAC, patients without proper DCE-MRI follow-up after NAC, and patients with poor DCE-MRI image quality (motion artifacts or insufficient contrast) were also

excluded. The patient selection criteria are shown in Figure 1.

### **NAC**

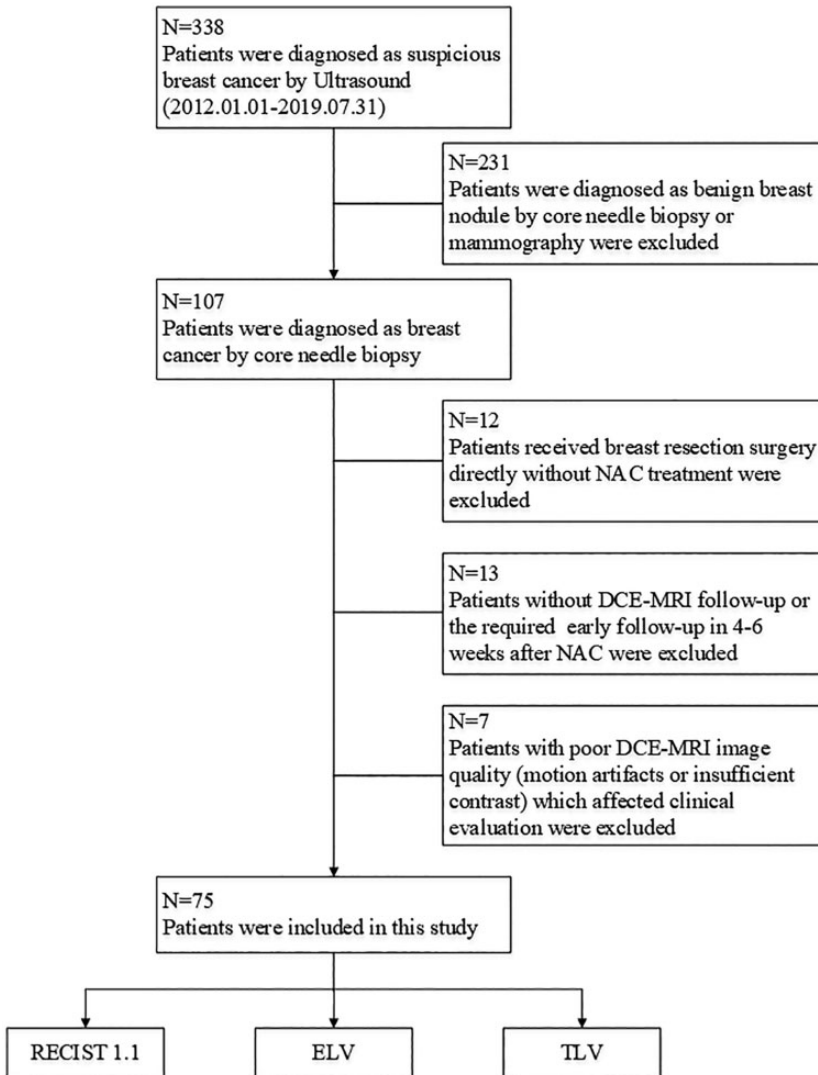
Patients were treated with different NAC regimens according to pathological subtype.

### *DCE-MRI acquisition*

All patients underwent one baseline (within 1 week prior to first chemotherapy) and one follow-up DCE-MRI examination (after two cycles of NAC treatment, including early NAC) using a 3.0 T MRI scanner (Ingenia, Philips Healthcare, The Netherlands, or Signa HDXT, General Electric Healthcare, WI, USA) equipped with an open digital coil. The baseline and follow-up scans for each patient were performed using the same scanner and same imaging protocol, including T1-weighted DCE-MRI series (TR 4.3 ms, TE 2.1 ms, layer thickness 1 mm, layer spacing  $-0.5$ , matrix:  $280 \times 339$ , FOV 350 mm, flip angle:  $12^\circ$ ) and six phases including one unenhanced and five contrast-enhanced phases (0.5 mmol/kg guanidine diamine intravenous) (General Electric Co. Ltd., Shanghai, China). The interval between two contrast-enhanced phases was 58 s for the Philips scanner and 108 s for the Signa scanner. The first phase without contrast was used as the pre-contrast image, and the phase with the most-enhanced lesion was used as the post-contrast image, which was usually the second or third phase. These pre- and post-contrast images were used for subsequent image processing and therapy response evaluation.

### *Image processing and calculation*

All the patients' data were transferred to a dedicated workstation (IntelliSpace Portal Version 9, Philips Healthcare). The pre-contrast and contrast-enhanced images at



**Figure 1.** Patient selection criteria.

NAC, neoadjuvant chemotherapy; DCE-MRI, dynamic contrast-enhanced magnetic resonance; ELV, enhancing lesion volume; TLV, total lesion volume.

baseline and follow-up were used to evaluate tumor response according to the tumor change percentage (TCP), defined as follows:

$$\text{TCP} = \frac{\text{Value}_{\text{post-NAC}} - \text{Value}_{\text{pre-NAC}}}{\text{Value}_{\text{pre-NAC}}} \times 100\%$$

where  $\text{Value}_{\text{pre-NAC}}$  was measured on the DCE-MRI images before NAC, and  $\text{Value}_{\text{post-NAC}}$  was measured on the follow-up DCE-MRI images after early NAC.

Tumor segmentation was performed using an intelligent three-dimensional (3D) semiautomatic segmentation tool in the Philips IntelliSpace Portal platform.

This 3D segmentation tool is based on the theory of radial basis functions and non-Euclidean geometry for semiautomatic segmentation of targets.<sup>34</sup> It allows the user to define a seed point and then expand the volume of the target in 3D by dragging the mouse toward the target boundary in a fully interactive way. The user can also draw the 3D contour of the target manually, and the segmentation result can be corrected if necessary. The volumetric segmentation accuracy has been reported and verified in previous studies.<sup>2,35,36</sup>

Image processing was carried out as follows. i) Registration: Pre-contrast and post-contrast images at baseline and follow-up were imported into the software platform. The images were registered automatically using a rigid registration algorithm between the intra- and inter-anatomical series. Users could adjust the position and orientation of the images slightly for more accurate registration, which could affect the measurement of the contrast-enhanced area. ii) Segmentation: The above smart semiautomatic 3D segmentation tool was used to define the target lesion on the breast on contrast-enhanced images at baseline, and the segmentation contour was then automatically propagated to the pre-contrast image at baseline and the pre- and post-contrast images at follow-up. Pathological lymph nodes associated with the breast cancer were defined, if they existed, and used for RECIST 1.1 evaluation. The maximum axial diameter and volume of the target lesions were calculated automatically after segmentation. iii) Enhancement calculation: A 3D region of interest (ROI, 1 cm × 1 cm × 1 cm) was placed on the hypo-enhancing ipsilateral pectoralis major and used as a reference to compute a normalized threshold of tissue contrast enhancement.<sup>3</sup> The viable enhancing tumor region was identified as voxels within the segmented tumor in a previous step with contrast enhancement greater

than two standard deviations of the reference ROI.<sup>37,38</sup> Non-enhancing and hypo-enhancing regions were considered to be necrotic and unviable. The TLV was represented as the total volume of viable enhancing tumor regions in cubic centimeters. This step was repeated in the follow-up studies. iv) Color map generation: A color map was generated and overlaid on the post-contrast-enhanced image to provide a visual demonstration of the volumetric and regional tumor enhancement heterogeneity. The color map for each patient was normalized to the maximum intensity of the baseline DCE-MRI scan, with red representing maximum (viable tumor) and blue indicating minimum enhancement (necrotic region). This step was repeated in the follow-up studies, using the same scale as that used at baseline.

### *Tumor response evaluation*

According to the RECIST 1.1 guidelines,<sup>29</sup> the RECIST 1.1 value was calculated as the sum of the longest axial diameter of the target tumor and the shortest axial diameter of the target lymph nodes. Tumor response evaluation was classified into four categories: progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). For RECIST 1.1, CR was identified when all the target lesions disappeared, PR as a decrease of at least 30% in the RECIST 1.1 value compared with baseline, PD as an increase of at least 20% in the RECIST 1.1 value, or SD with insufficient increase for PD and insufficient shrinkage for PR. RECIST 1.1 only took account of changes in the maximum diameter and was therefore considered as a one-dimensional (1D) method.

The TLV value was defined as the total volume of all the target lesions, and the ELV value was considered as the sum of the enhancing volume of all the target lesions. These two methods evaluated

tumor response in a 3D manner. Mathematically, a 30% decrease in diameter may result in an approximately 65% decrease in volume, and a 20% increase in diameter may result in an approximately 73% increase in volume. PR in TLV and ELV was therefore defined as a decrease of 65% compared with baseline, and PD as an increase of 73% compared with baseline<sup>39</sup> (Figure 2).

Image processing and tumor measurement were performed independently and then averaged by two radiologists with >1 year of experience with the software, who were blinded to the patient information and not involved in NAC treatment. Any discrepancies were resolved by consensus. A third radiologist performed the tumor response evaluation based on RECIST 1.1, TLV, and ELV.

All cases identified as CR or PR were defined as responders, and those with SD or PD were considered as non-responders.<sup>31</sup>

### Pathological evaluation

All patients underwent mastectomy after NAC. The specimens were cut into 5-mm slices and then fixed with 10% neutral formalin buffer for histological examination. If the tumor was visible to the naked eye, the

maximum diameter of the tumor was measured and paraffin sections containing the tumor were stained with hematoxylin and eosin for pathological evaluation. Otherwise, residual tissue markers within the breast were detected, and slices containing the markers and the adjacent slices were examined.<sup>40</sup> The results were compared with reference to the pathological results using the Miller–Payne system, with the following histological classification: Grade 1: no change, no significant reduction in malignant cells; Grade 2: minor loss of tumor cells ( $\leq 30\%$ ); Grade 3: reduction in tumor cells between 30% and 90%; Grade 4: disappearance of tumor cells  $>90\%$ ; and Grade 5: no malignant cells identifiable, ductal carcinoma *in situ* may be present. Patients with Grade 4/5 were categorized as pathological responders and those with Grade 1/3 were considered as pathological non-responders.<sup>41,42</sup>

### Statistical analysis

All continuous variables (maximum diameter, total lesion volume, and enhancing lesion volume) were reported as mean  $\pm$  standard deviation. Categorical values (case numbers with tumor therapy response results as PD, SD, PR, and CR) were

	RECIST 1.1	TLV	ELV
CR	Disappearance of all target lesions	Disappearance of all target lesions	Disappearance of all enhancing tissue in all target lesions
PR	$\geq 30\%$ decrease in the sum of the longest axial diameter of the target lesions and the shortest axial diameter of the target lymph nodes	$\geq 65\%$ decrease in the sum of the volume of the target lesions	$\geq 65\%$ decrease in the sum of enhancing tissue volume of the lesions
SD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
PD	$\geq 20\%$ increase in the sum of the longest axial diameter of the target lesions and the shortest axial diameter of the target lymph nodes	$\geq 73\%$ increase in the sum of the volume of the target lesions	$\geq 73\%$ increase in the sum of enhancing tissue volume of the lesions

**Figure 2.** Evaluation methods used to assess tumor therapy response.

TLV, total lesion volume; ELV, enhancing lesion volume; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.



expressed as frequencies and percentages. Differences between pre- and post-NAC measurements using the three tumor response methods were evaluated by Wilcoxon's test. TCP values for the three evaluation methods pre-and post-NAC were compared using the Friedman test. Differences in tumor therapy response results among the three methods were compared using the  $\chi^2$  test and pairwise comparisons were performed using the McNemar and kappa ( $\kappa$ ) tests. A  $\kappa$  value of 0.0 to 0.20 represented slight consistency, 0.21 to 0.40 fair consistency, 0.41 to 0.60 moderate consistency, 0.61 to 0.80 good consistency, and  $>0.8$  implied almost perfect consistency. The pathologic response results, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of each method for response evaluation were calculated. The TCP values of the three methods were analyzed using receiver operating characteristic (ROC) curves, and the overall performances were compared based on the areas under the ROC curves (AUC).  $P < 0.05$  was considered statistically significant. All statistical analyses were performed using MedCalc software Bvba (Version 18, MedCalc, Belgium) and the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

## Results

### *Patients and treatments*

A total of 338 patients at our hospital had suspected breast cancer from January 2012 to July 2019. Of these, 231 diagnosed with benign breast nodules were excluded. A further 12 patients who received surgery without NAC treatment, 13 patients without proper DCE-MRI follow-up after NAC, and seven patients with poor DCE-MRI image quality (motion artifacts or insufficient contrast) were also excluded.

Seventy-five patients were finally included in our study. Each patient only had one unilateral lesion, and results for 75 target lesions were therefore analyzed.

These 75 patients with breast cancer were treated with different NAC regimens according to pathological subtype, as follows: 21 patients received AC-T (doxorubicin and cyclophosphamide, followed by docetaxel) combination chemotherapy with four cycles of doxorubicin ( $60 \text{ mg/m}^2$ ) and cyclophosphamide ( $600 \text{ mg/m}^2$ ) followed by four cycles of docetaxel ( $100 \text{ mg/m}^2$ ). Twenty-eight patients who were identified as HER2-positive were treated with AC-TH (doxorubicin and cyclophosphamide, followed by paclitaxel and trastuzumab) combination chemotherapy with four cycles of doxorubicin ( $60 \text{ mg/m}^2$ ) and cyclophosphamide ( $600 \text{ mg/m}^2$ ), followed by four cycles of docetaxel ( $100 \text{ mg/m}^2$ ) and trastuzumab (initial dose of  $8 \text{ mg/kg}$ , second dose of  $6 \text{ mg/kg}$ , once every 3 weeks, for 1 year). Nineteen patients received TAC (taxotere/docetaxel, adriamycin/doxorubicin, and cyclophosphamide) chemotherapy with six cycles of docetaxel ( $75 \text{ mg/m}^2$ ), doxorubicin ( $50 \text{ mg/m}^2$ ), and cyclophosphamide ( $500 \text{ mg/m}^2$ ). The other seven patients with triple-negative breast cancer received TC (docetaxel and carboplatin) combination chemotherapy with six cycles of docetaxel ( $75 \text{ mg/m}^2$ ) and carboplatin (AUC 6 dL). Each chemotherapy cycle lasted for 3 weeks.

All 75 patients were female (average age  $49 \pm 10$  years, range 33–73 years). Fifty-six patients were classified with stage II and 19 patients with stage III. Sixty-eight patients had invasive ductal carcinoma (90.7%), two had invasive lobular carcinoma (2.7%), two had ductal carcinoma *in situ* (2.7%), and three patients had mucinous carcinoma (4.0%). Twenty-six patients had lymph node metastasis and 49 had no lymph node metastasis. Pathological results based on the Miller–Payne system identified 10

cases as Grade 1, 12 as Grade 2, 28 as Grade 3, 18 as Grade 4, and seven as Grade 5. The 25 patients with Grade 4/5 were considered to be pathological responders, and the other 50 cases were considered to be pathological non-responders.

### *Tumor therapy responses based on RECIST 1.1, TLV, and ELV methods*

The baseline and follow-up measurements, and the TCP values for the RECIST 1.1, TLV, and ELV methods are displayed in Table 1. Lesions were reduced soon after receiving NAC according to all three evaluation methods (all  $P < 0.005$ ). However, the TCP value for RECIST 1.1 was less than that for TLV and ELV, with significant differences among the three methods ( $F = 43.19$ ,  $P < 0.01$ ).

The tumor therapy responses of the 75 breast lesions based on RECIST 1.1, TLV, and ELV are displayed in Table 2. No cases were defined as CR in by any of the three methods, but 15, 17, and 22 were defined as PR based on RECIST 1.1, TLV, and ELV, respectively. The number of patients with SD was the same according to RECIST

1.1 and TLV, and was higher than the result based on ELV. Only a few cases were evaluated as PD by all three methods. There was no significant difference among the three methods.

Pairwise comparisons of tumor therapy response evaluation results among the three methods are presented in Table 3. There was no significant difference in pairwise comparisons of the three methods in terms of tumor therapy response evaluation. Based on the  $\kappa$  test results, RECIST 1.1 showed moderate consistency with both ELV and TLV, while consistency between ELV and TLV was perfect.

### *Pathological tumor response*

The pathological evaluation results identified 25 responders and 50 non-responders. The diagnostic performances of the three methods are summarized in Table 4. The ELV method identified 22 responders, which was consistent with the pathological results in 18 of the 25 cases (72%). The TLV method classified 17 responders, which matched the pathology results in 14 cases (56%), and RECIST 1.1 categorized

**Table 1.** Measurements based on three different methods.

Evaluation method	Baseline	Follow-up	TCP (%)	Z value	P value
RECIST 1.1	34.70 ± 17.87	28.94 ± 14.52	-13.55 ± 18.96	5.59	<0.005
TLV	14.45 ± 26.51	8.79 ± 14.79	-32.84 ± 38.40	5.95	<0.005
ELV	10.16 ± 18.55	5.31 ± 8.63	-35.93 ± 46.49	6.21	<0.005

RECIST 1.1, response evaluation criteria in solid tumors 1.1; TLV, total lesion volume; ELV, enhancing lesion volume; TCP, tumor change percentage.

**Table 2.** Comparison of tumor therapy response evaluation by three methods.

Evaluation method	PR	SD	PD	$\chi^2$	P value
RECIST 1.1	15 (20%)	56 (75%)	4 (5%)	2.55	0.64
TLV	17 (23%)	56 (75%)	2 (3%)		
ELV	22 (29%)	50 (67%)	3 (4%)		

RECIST 1.1, response evaluation criteria in solid tumors 1.1; TLV, total lesion volume; ELV, enhancing lesion volume; PR, partial response; SD, stable disease; PD, progressive disease.



**Table 3.** Pairwise comparison of tumor therapy response evaluation results.

RECIST 1.1								
ELV	PR	11	11	0	$\chi^2$ 4.267	P value 0.118	$\kappa$ value 0.52	P value <0.001
	SD	4	45	1				
	PD	0	0	3				
TLV								
ELV	PR	17	5	0	$\chi^2$ 6.00	P value 0.05	$\kappa$ value 0.82	P value <0.001
	SD	0	50	0				
	PD	0	1	2				
TLV								
RECIST 1.1	PR	10	5	0	$\chi^2$ 2.333	P value 0.311	$\kappa$ value 0.53	P value <0.001
	SD	7	49	0				
	PD	0	2	2				

Comparisons between ELV and RECIST 1.1, ELV and TLV, and RECIST 1.1 and TLV.

RECIST 1.1, response evaluation criteria in solid tumors 1.1; TLV, total lesion volume; ELV, enhancing lesion volume; PR, partial response; SD, stable disease; PD, progressive disease.

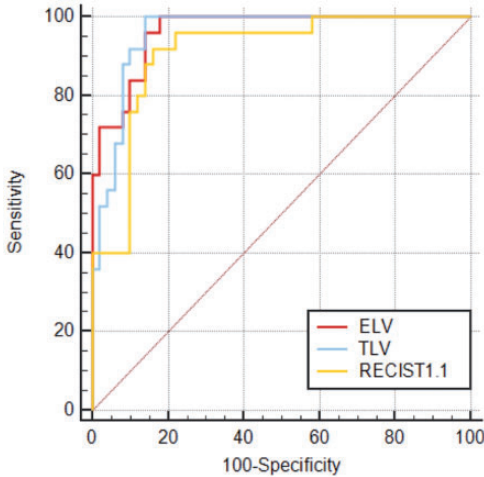
**Table 4.** Comparison of diagnostic performances of three evaluation methods with pathologic results between responders and non-responders.

		Pathologic finding		Total
		Responder	Non-responder	
ELV	Responder	18	4	22
	Non-responder	7	46	53
RECIST 1.1	Responder	11	4	15
	Non-responder	14	46	60
TLV	Responder	14	3	17
	Non-responder	11	47	58
Total		25	50	75
	ELV	RECIST 1.1	TLV	
Sensitivity (%)	72%	44%	56%	
Specificity (%)	92%	92%	94%	
PPV (%)	81.8%	73.3%	82.3%	
NPV (%)	86.8%	76.7	81.0%	
Accuracy (%)	85.3%	76%	81.3%	

RECIST 1.1, response evaluation criteria in solid tumors 1.1; TLV, total lesion volume; ELV, enhancing lesion volume; PPV, positive predictive value; NPV, negative predictive value.

15 patients as responders, which agreed with the pathology in 11 cases (44%). Regarding the prediction of pathologic response, the sensitivity, specificity, positive predictive value (PPV), negative predictive

value (NPV), and accuracy of the ELV method were 72%, 92%, 81.8%, 86.8%, and 85.3%, respectively. ELV had the highest sensitivity, NPV, and accuracy for diagnosis among the three methods.



**Figure 3.** Receiver operating characteristic curve analysis of the three methods.

ELV, enhancing lesion volume; TLV, total lesion volume.

### ROC curve analysis

The results of the ROC curve analysis are displayed in Figure 3. The AUCs for ELV, TLV, and RECIST were 0.962 (95% confidence interval (CI): 0.891–0.993), 0.957 (95%CI: 0.883–0.990), and 0.910 (95%CI: 0.821–0.964), respectively. The post-hoc pairwise comparison results based on the ROC curves were as follows: ELV versus RECIST 1.1 ( $z=1.672$ ,  $P=0.09$ ); ELV versus TLV ( $z=0.273$ ,  $P=0.78$ ); and TLV versus RECIST 1.1 ( $z=1.293$ ,  $P=0.19$ ). According to the definition of PR in Figure 2, the sensitivity and specificity of RECIST 1.1 were 40% (95%CI: 21.1–61.3) and 90% (95%CI: 78.2–96.7), respectively, with a threshold of approximately. Using thresholds of approximately  $-65\%$ , the sensitivities and specificities of the ELV and TLV methods were 72% (95%CI: 50.6–87.9) and 92% (95%CI: 80.8–97.8), and 56% (95%CI: 34.9–75.6) and 94% (95%CI: 83.5–98.7), respectively.

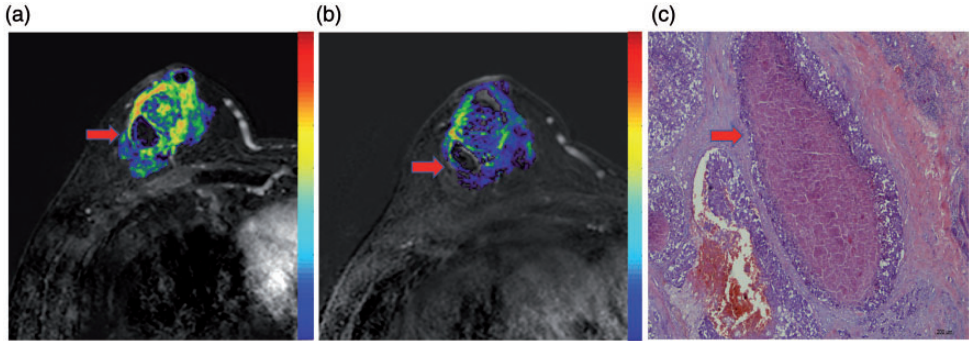
### Color maps

We also evaluated the color maps generated based on contrast enhancement with pathological necrosis. The color maps represented tumor blood supply, which in turn indicated the cellular activity of the lesions, which may indirectly help to evaluate the tumor response after receiving treatment. Comparing the color maps before and after chemotherapy (Figure 4) showed that the blood flow signal of the target lesions was significantly diminished after chemotherapy, suggesting reduced tumor activity, as demonstrated by the corresponding pathological results. A previous study suggested that the response should be more prominent in tumors with high heterogeneity because of a better blood supply that facilitates chemotherapy in the early cycles.<sup>25</sup>

### Discussion

Previous clinical experience and some relevant studies<sup>30,31,40,42</sup> have shown that the evaluation of tumor treatment response after early NAC may directly affect the selection of treatment methods and chemotherapy regimens for breast cancer patients by clinicians, highlighting the importance of accurate response evaluation after early NAC. ELV takes account of morphological changes in tumor size as well as changes in cell activity within the tumor, suggesting that it could be a promising tool for evaluating tumor therapy response.

The present study found no significant difference among RECIST 1.1, TLV, and ELV in terms of tumor therapy response evaluation. This may be because most tumors had responded well to two cycles of early NAC after 4 to 6 weeks, and most patients were therefore diagnosed with PR or SD, with very few cases of PD according to any of the three methods. The frequency of PR was highest using the ELV



**Figure 4.** Images of a 52-year-old patient who demonstrated heterogeneous tumor enhancement observed on color maps and pathological slices. (a) Color map from pre-neoadjuvant chemotherapy (NAC) post-contrast dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI); (b) color map from post-NAC post-contrast DCE-MRI image; (c) pathological slice (magnification  $\times 20$ ). Much of the viable tumor became less enhanced after NAC and appeared blue in the post-treatment color map. The necrotic area indicated by the red arrow in the color map of the lesion post-NAC was consistent with the necrotic area shown by the red arrow in the pathological results. The color bar indicated gradually decreasing lesion activity, from red to blue.

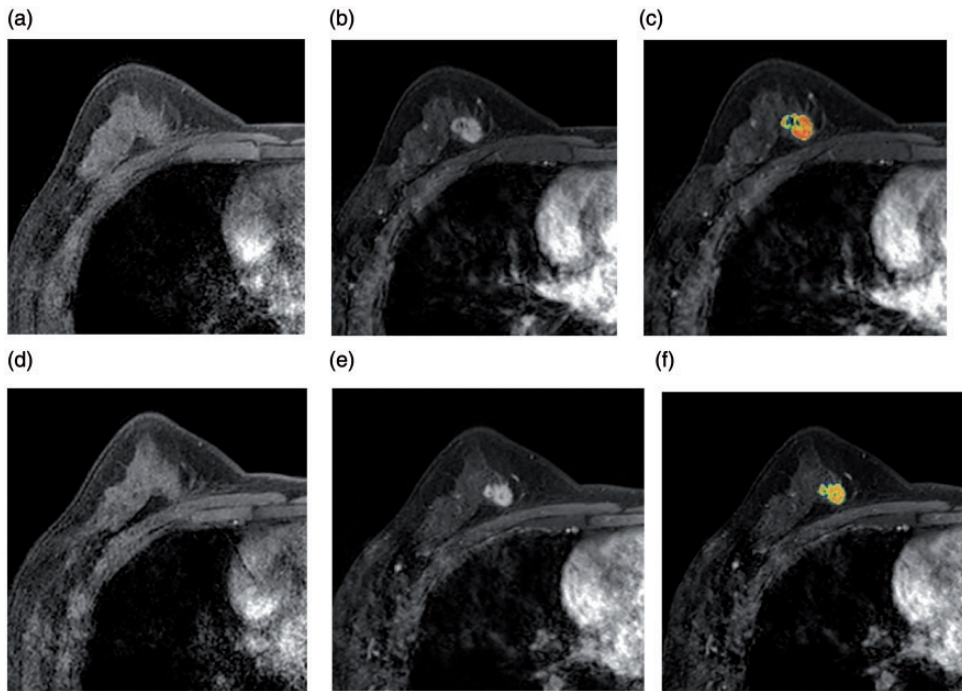
method and lowest using the RECIST 1.1 criteria, probably because the contours of most tumors were irregular, the morphology and internal density may change, or hollow areas may even appear within the tumor after the treatment. These factors mean that tumor burden could not be accurately evaluated based on changes in maximum diameter measured in 1D.

Pairwise comparisons of the three methods also found no significant difference in tumor therapy response assessed by the three methods, suggesting that ELV and TLV may be feasible methods for evaluating tumor response, with RECIST 1.1 as the reference. A sample case evaluated as SD by all three methods is shown in Figure 5. In addition, the evaluation results of ELV and TVL showed excellent consistency ( $\kappa > 0.8$ ), which was significantly higher than the other two  $\kappa$  values (approximately 0.5). This is probably because both ELV and TLV evaluated the changes in tumor size in 3D, while RECIST 1.1 only considered the change in 1D.

In terms of predicting pathological response, ELV and TLV both had higher

sensitivity, specificity, PPV, NPV, accuracy, and AUC compared with RECIST 1.1. According to ROC analysis, ELV had higher sensitivity and equal specificity compared with TLV and RECIST 1.1 using a threshold value of  $-65\%$  for both ELV and TLV and  $-30\%$  for RECIST 1.1, based on the definition of PR. Furthermore, the color map generated by the ELV method provided a visual representation of the cellular activity and heterogeneity within the tumor after chemotherapy. Some cases in this study showed no obvious changes in maximum tumor diameter, but necrosis, cystic degeneration, or fibrosis were observed in pathological slices (Figure 6). These may be misidentified by RECIST 1.1 and TLV, which only considered morphological changes in tumor size or volume. Some studies analyzed and compared the difference between 3D and 1D measurements and proposed that 3D measurements could reduce the overall errors by averaging the errors for each slice of the lesions.<sup>42</sup>

The simplified working process using an intelligent software platform allowed the image processing and calculation processes



**Figure 5.** Images of a 44-year-old patient with no lymph node metastasis with tumor evaluation results based on RECIST 1.1, TLV, and ELV methods from pre-neoadjuvant chemotherapy (NAC) ((a) pre-contrast image; (b) post-contrast image; (c) post-contrast image overlaid with color map) and post-NAC dynamic contrast-enhanced-magnetic resonance imaging ((d) pre-contrast image; (e) post-contrast image; (f) post-contrast image overlaid with color map). Longest length decreased by 10.65% (from 26.3 to 23.5 mm) after NAC, total volume decreased by 10.65% (from 3.66 to 3.26 mm<sup>3</sup>), and enhanced volume decreased by 59.29% (from 3.25 to 1.32 mm<sup>3</sup>) after NAC, were all defined as SD. The evaluation results were the same for all three methods.

RECIST 1.1, response evaluation criteria in solid tumors 1.1; TLV, total lesion volume; ELV, enhancing lesion volume.

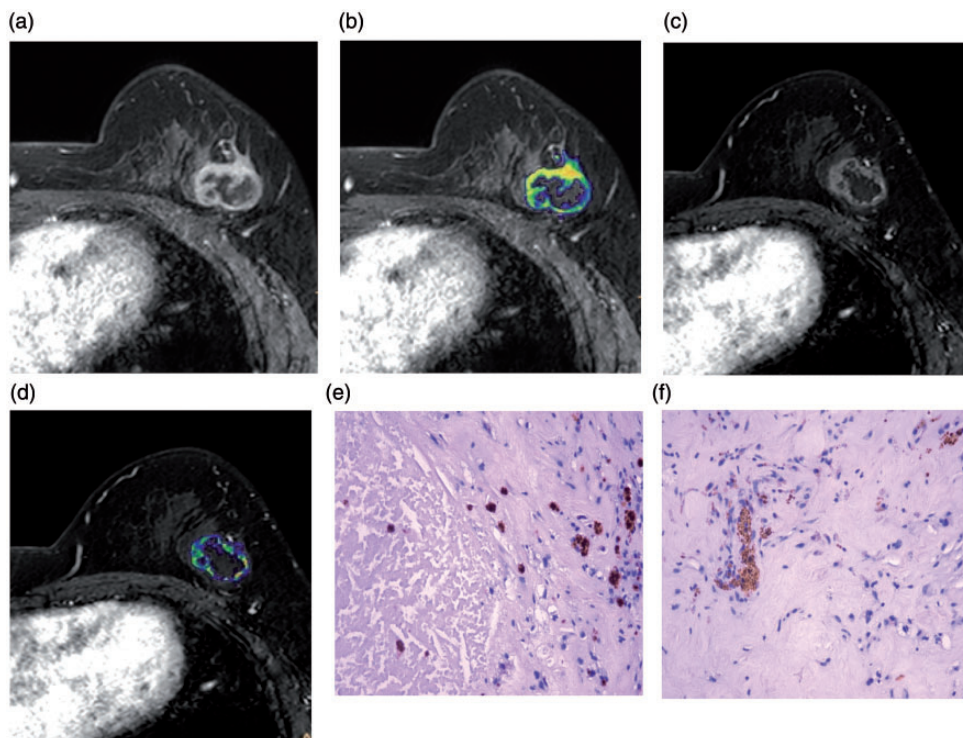
to be carried out quickly, with high accuracy and repeatability, thus avoiding or reducing the errors associated with manual measurements. After lesion segmentation on pre- and post-contrast MRI images obtained before and after early NAC treatment, the measurements for RECIST 1.1, TLV, and ELV were presented automatically, allowing the user to view the tumor response results of the three methods simultaneously. The segmentation performance of the 3D semiautomatic tool has been proven in previous studies,<sup>36,43</sup> while other studies<sup>42,44,45</sup> showed that the 3D quantitative enhancing volume method

could be used to evaluate treatment efficacy for other solid tumors after transarterial chemoembolization or radiofrequency ablation.

This study had some limitations. First, few patients were diagnosed with PD. Second, it was an early NAC study and the follow-up time was only 4 to 6 weeks after the start of NAC treatment. Finally, the sample size was relatively small. Further studies with more cases are therefore needed to verify these findings.

In conclusion, ELV, TLV, and RECIST 1.1 criteria showed similar abilities for





**Figure 6.** Images of a 48-year-old patient with no lymph node metastasis with tumor evaluation results based on RECIST 1.1, TLV, and ELV methods from pre-neoadjuvant chemotherapy (NAC) ((a) post-contrast image; (b) post-contrast image overlaid with color map) and post-NAC dynamic contrast-enhanced-magnetic resonance imaging ((c) post-contrast image; (d) post-contrast image overlaid with color map). Maximum diameter decreased by 7.69% (from 35.10 to 32.40 mm) after NAC, defined as SD, total volume decreased by 34.3% (from 15.8 to 10.38 mm<sup>3</sup>) after NAC, defined as SD, and enhanced volume decreased by 66.03% (from 10.97 to 3.74 mm<sup>3</sup>) after NAC, defined as PR. The pathological results clearly showed that the tumor responded to chemotherapy. Paraffin sections containing the tumor (magnification  $\times 20$ ) showing necrotic and fibrotic tumor cells (decreased by 90% after NAC, Grade 4) (e) and some areas with hyaline degeneration (f), consistent with the evaluation of PR based on ELV (hematoxylin and eosin). RECIST 1.1, response evaluation criteria in solid tumors 1.1; TLV, total lesion volume; ELV, enhancing lesion volume.

evaluating tumor therapy response in breast cancer patients after early NAC. ELV may thus be a feasible option for evaluating the responsiveness of breast cancer patients to early NAC on DCE-MRI images. Regarding the prediction of pathological response, ELV demonstrated the best diagnostic performance with the highest sensitivity, NPV, accuracy, and AUC value. In addition to these quantitative measurements, visual analysis using a color map

may provide functional information in addition to morphological changes after chemotherapy. This preliminary study suggested that ELV may be a better tumor-response indicator than the current RECIST 1.1 criteria, because of its ability to consider the vital tumor burden in breast cancer. In addition, the easy-to-apply procedures and measurements involved were semiautomatic, thus minimizing human error and bias.


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The authors declare that there is no conflict of interest.

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