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# A new algorithm for automatic vascular mapping of DCE-MRI of the breast: Clinical application of a potential new biomarker

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## ABSTRACT

**Background and objective:** Vascularity evaluation on breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has a potential diagnostic value, but it represents a time consuming procedure, affected by intra- and inter-observer variability. This study tests the application of a recently published method to reproducibly quantify breast vascularity, and evaluates if the vascular volume of cancer-bearing breast, calculated from automatic vascular maps (AVMs), may correlate with pathologic tumor response after neoadjuvant chemotherapy (NAC).

**Methods:** Twenty-four patients with unilateral locally advanced breast cancer underwent DCE-MRI before and after NAC, 8 responders and 16 non-responders. A validated algorithm, based on multiscale 3D Hessian matrix analysis, provided AVMs and allowed the calculation of vessel volume before the initiation and after the last NAC cycle for each breast. For cancer bearing breast, the difference in vascular volume before and after NAC was compared in responders and non-responders using the Wilcoxon two-sample test. A radiologist evaluated the vascularity on the subtracted images (first enhanced minus unenhanced), before and after treatment, assigning a vascular score for each breast, according to the number of vessels with length  $\geq 30$  mm and maximal transverse diameter  $\geq 2$  mm. The same evaluation was repeated with the support of the simultaneous visualization of the AVMs. The two evaluations were compared in terms of mean number of vessels and mean vascular score per breast, in responders and non-responders, by use of Wilcoxon two sample test. For all the analysis, the statistical significance level was set at 0.05.

**Results:** For breasts harboring the cancer, evidence of a difference in vascular volume before and after NAC for responders (median = 1.71 cc) and non-responders (median = 0.41 cc) was found ( $p = 0.003$ ). A significant difference was also found in the number of vessels ( $p = 0.03$ ) and vascular score ( $p = 0.02$ ) before or after NAC, according to the evaluation supported by the AVMs.

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*Conclusions:* The encouraging, although preliminary, results of this study suggest the use of AVMs as new biomarker to evaluate the pathologic response after NAC, but also support their application in other breast DCE-MRI vessel analysis that are waiting for a reliable quantification method.

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## 1. Description of purpose

Solid tumors rely on blood vessels to obtain necessary nutrient and oxygen, and new vessels also offer path way for tumor expansion. Therefore, the assessment of tumor vascularity may provide useful information to characterize underlying malignancy and monitor vascular abnormalities [1]. In the past decade, microvessel density represented the most commonly used prognostic indicator for tumor vascularization in a wide range of cancers, although its quantification remained unreliable because of the lack of sufficient morphological and functional information of blood vessels, and it could be only assessed after the surgical resection of the primary tumor [1]. A better alternative to study tumor vasculature may be derived from non-invasive imaging techniques, such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), positron emission tomography (PET), and more recently, B-mode and Doppler ultrasound (US). With varied types of cancer, there is no general agreement as to which established imaging method is most suitable for determining features of tumor blood vessels [1].

Breast DCE-MRI has emerged as the most sensitive technique for the detection and diagnosis of breast lesions and numerous studies have confirmed the superior performance of MRI compared with mammography and ultrasound (US), leading to its recommendation for several indications, such as in the surveillance of women with high risk of breast cancer and in the clinical workup of patients with carcinoma unknown primary (CUP) syndrome [2,3]. Moreover, MRI showed advantages over conventional imaging modalities in monitoring the tumor response to neoadjuvant treatments [4], also because of its capability to detect changes in vascularity due to chemotherapeutic agents, including anti-angiogenics [5,6]. MRI has the potential to tailor surgical planning of patients with breast cancer, although its impact on clinical outcomes is still on debate. In addition, some reports suggest that preoperative breast MRI in women with newly diagnosed cancer could potentially increase the rate of unnecessary biopsies and surgery [2]. Recent studies aimed to increase the specificity of breast DCE-MRI by adding a vessel analysis to the standard morphologic and kinetic criteria, therefore exploring the diagnostic value of vascularity [7–9]. During the past decade, this research issue has been approached in two ways: first, whole-breast vascularity, and second, local vascularity, that is, vessels adjacent to and feeding a lesion or lesions [9]. The evaluation of this information is already allowed, since the visualization of bilateral vascular maps is intrinsically integrated into a standard breast DCE-MRI study without an increase in acquisition time or the administration of

additional contrast material [9,10]. However, vascularity is not usually considered by radiologists, mainly because evaluating and counting vessels using multiple views may be time consuming and a standardized quantification method of breast vessels does not exist [10]. Several studies have tried to address the automatic detection and extraction of the breast vascularity to improve the work-flow of radiologists [1,11,12], but only one of them has been conceived to work on DCE-MRI [13]. However, the last method, proposed by Lin et al. and based on wavelet transform and the Hessian matrix, is affected by some limitations. Indeed, it relies on a preliminary manual interaction while breast lesions are excluded by placing a square box over the lesion, and it has been tested on patients with relatively large lesions, large vessels, and no motion artifacts on subtracted images. Regarding the evaluation of the vascularity in the clinical practice, the unique quantitative approach existing has been introduced by Sardanelli et al. [7] and it is based on the number of vessels per breast, with length of 30 mm or greater and maximal transverse diameter of 2 mm or greater. This method was used by a recent study [10] to assess the variation in whole-breast vascular maps on DCE-MRI after anthracycline- and taxane-based neoadjuvant chemotherapy (NAC) in patients with locally advanced breast cancer (LABC), showing a correlation between changes in breast vascular maps and pathologic tumor response. However, the authors highlight some limitations of the Sardanelli score system, as also recognized by other authors [14], such as difficulties in counting branching vessels, and time-consuming procedure to define if a vessel should or should not be counted. The development of a highly reproducible method to extract vascular maps and to quantify vessels within the breast has been therefore encouraged [9,10]. In 2012, our group developed a novel fully automatic Hessian-matrix method able to overcome the limitations of Lin et al. approach [15]. The aim of the present study is to test the application of our recently published method to reproducibly quantify breast vascularity, and to evaluate if the vascular volume of cancer-bearing breast, calculated from automatic vascular maps (AVMs), may correlate with pathologic tumor response after NAC.

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## 2. Methods

The dataset was composed by 24 patients (mean age, 46 years; range 31–61) with unilateral LABC diagnosed at mammography and/or ultrasound. For each patient, DCE-MRI was performed before NAC initiation and repeated after the last NAC cycle. Breast surgery was scheduled within 3–4 weeks after the last NAC cycle. After surgery, the histopathologic response was evaluated using a 5-point assessment scale, from grade 1 (some alterations to individual malignant cells

but no reduction in overall numbers compared with the pre-treatment core biopsy) to grade 5 (pCR; pathologic complete response) [16]. In the current study, the patients were classified as responders if the pathologic tumor response to primary chemotherapy was grade 4 or 5 and as non-responders if the grade of response ranged between 1 and 3.

DCE-MRI was performed using a 1.5-T scanner (Signa Excite Hdx, GE Healthcare) with a dedicated 8-channel coil with the patient in prone position. A 3D gradient-echo axial sequence (Vibrant, GE Healthcare) was performed with the following technical parameters: TE in phase; TR/TE, 5.4/2.6; flip angle, 15°; slice thickness, 2.6 mm; matrix, 416 × 416; field of view, according to the breast volume; and temporal resolution, 60–90 s depending on the volume of the breasts. The sequence was performed before and four times continuously after contrast material administration; a late acquisition was obtained at 8 min after contrast material administration. The contrast-enhanced study started simultaneously with the bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist, Bayer Pharma) at a rate of 2 mL/s, followed by a saline flush of 20 mL at the same injection rate. The Local Ethics Committee approved the retrospective use of the database for scientific purposes and waived off informed consent. The study was conducted in accordance with national legislation and the Declaration of Helsinki.

Breast AVMs were extracted by the application of a fully automatic multiscale 3D Hessian matrix-based algorithm for vessel detection in breast DCE-MRI [15]. This algorithm is conceived as a 2-step process to search for geometrical tube-like structures (Fig. 1), starting from the isotropic subtraction images. In particular, in order to obtain the best “angiographic effect” for both arteries and veins [7], the subtraction was performed between the first enhanced frame and the unenhanced frame.

The first step, aiming to detect linear structures, is composed of a multi-scale analysis, and successive volume integration, while in the second step non-vessel detected voxels are reduced according to the analysis of the covariance matrix.

### 2.1. First step: multi-scale analysis

To extract vessels of different dimensions, a measurement scale which varies within a set range was introduced by applying a Gaussian blur filter using 5 different standard deviations ( $\sigma$ ), so that 5 subimages smoothed with increasing  $\sigma$  size were obtained. Since the  $\sigma$  of Gaussian blur and vessel dimension are related according to [17]:

$$\sigma = r\sqrt{2},$$

the  $\sigma$  values ranged from 0.80 ( $\sigma_0$ ) to 1.00 ( $\sigma_4$ ), within a step of 0.05, allowing to extract vessels of diameter >1 mm. In order to enhance and extract vessels on each smoothed image, the morphology of curvilinear structures was assessed via eigenvalue analysis of the Hessian matrix. After setting all positive eigenvalues to zero, the smallest eigenvalue was subtracted from the largest eigenvalue, allowing to distinguish linear structures, which have positive values, from nodular structures, having values that approximate zero [13,18]. For a fair

comparison of images at multiple scales, for each scale the obtained subimage was multiplied by the respective  $\sigma$  value (normalization).

### 2.2. First step: volume integration

To integrate information from the multi-scale analysis, the maximum intensity projection (MIP) of the five subimages was performed. To compensate for the dependence on the breast, vessels and lesion extension of a cumulative histogram based threshold, the obtained MIP was dichotomized according to a threshold automatically calculated from the mammary vessel region. A suitable ROI of a fixed size (50 mm × 100 mm) was automatically selected in the region of mammary vessels of the MIP according to Vignati et al. [19] method, and 99% of the cumulative histogram of the ROI was chosen as the threshold to extract vessel-like structures.

### 2.3. Second step: reduction of the number of non-vessel detected voxels

The binary mask obtained at the end of the first step still contained some non-vessel structures, such as noise components and irregular margins of lesions. These regions have a blob-like structure with an elongated shape, characterized by positive values when minimum Hessian eigenvalues are subtracted from maximum Hessian eigenvalues. The covariance matrix was studied as a morphological descriptor of a region in terms of the extension along its principal component. For each voxel defined as a vessel by the first step, the covariance was evaluated in an 8 mm-radius volume of interest. The eigenvectors of the covariance matrix indicate the principal direction of the analyzed region, and the eigenvalues represent the variance of the voxel coordinates along each eigenvector. In this analysis, only the maximum ( $\lambda_3$ ) and minimum ( $\lambda_1$ ) eigenvalues of the covariance matrix were considered, because they make it possible to distinguish between linear ( $\lambda_3 \gg \lambda_1$ ) and elongated blob-like ( $\lambda_3 > \lambda_1$ ) structures. A threshold was applied to the ratio between maximum and minimum eigenvalue, and only objects with ratio >7 were considered. Finally, objects with an area <10 mm<sup>3</sup> were discarded in order to exclude small isolated structures not connected to other vessel voxels (morphological filter).

The algorithm provides a 3D vascular map automatically excluding the lesions. By multiplying each vascular map voxel by its volume, the automatic vessel detection method was used to calculate the vessel volume before the initiation and after the last NAC cycle for each breast. For breasts harboring the cancer, the difference in vascular volume before and after neoadjuvant treatment was compared in responders and non-responders using the Wilcoxon two-sample test.

A radiologist with 7 years of experience with breast MRI, blinded to final pathologic analysis, evaluated the breast vascularity on the subtracted images. For each examination, in both breasts, length and diameter of vessels were manually measured using electronic calipers, and a vascular score per breast was assigned. Four grades of breast vascularity were defined, ranging from 0 to 3, according to the number of vessels that were 30 mm or greater in length and 2 mm or greater in maximal transverse diameter. Subsequently, the

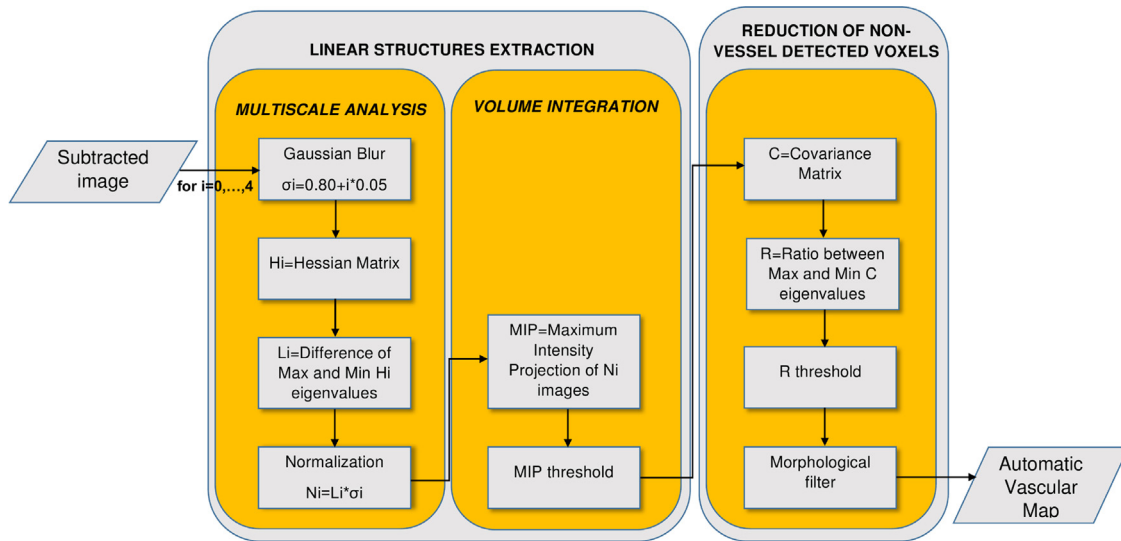


Fig. 1 – Pipeline of the vessel extraction algorithm.

radiologist was asked to re-evaluate the breast vascular maps and re-assign the vascular score per breast, with the support of the simultaneous visualization of the AVMs produced by the algorithm. The results of both evaluations were compared in terms of mean number of vessels and mean vascular score per breast, before and after NAC. The mean number of vessels and the mean vascular score after NAC were also compared in responders and non-responders. The groups were compared by use of Wilcoxon two sample test. The radiologist further analyzed the images of patients in which the two evaluations recorded a different number of vessels. For all the analysis, the statistical significance level was set at 0.05.

### 3. Results

Eight patients were classified as responders: four with grade 5 response (pCR), and four with grade 4 response. For breasts harboring the cancer, considering both responders and non-responders, the median value of the difference in vascular volume before and after neoadjuvant treatment was 1.01 cc (1st–3rd quartiles 0.27–1.47 cc), while in the contralateral breasts it was 0.09 cc (1st–3rd quartiles –0.05 to 0.46 cc).

Both vascular evaluations performed by the radiologist, with and without support of the AVMs, show a significant reduction ( $p < 0.05$ ) of the number of vessels and vascular score after NAC for breasts bearing cancer in respect to contralateral breasts. In Table 1 are reported the values of volume difference, difference of number of vessels, and vascular score difference after NAC for cancer bearing breasts divided in responders and non-responders, for both evaluations (with and without the support of the automatic maps).

Considering the number of vessels and the vascular score before NAC or after NAC, no significant difference was found in the evaluation performed without support of the AVMs, while significant difference was found according to the evaluation supported by the AVMs.

The analysis of cases in which the number of vessels was different between the two evaluations stated that the

automatic vascular mapping helps in correctly detect breast vessels according to the diameter, especially near the end of a vascular tree or when a low intensity may complicate the evaluation.

Figs. 2 and 3 show the MIP of the subtraction image and the AVMs before and after NAC, respectively for a responder and a non-responder patient.

### 4. Discussion

The added diagnostic value of local and global breast vascularity has been recently investigated [9] and preliminary results have shown that breast vascular maps obtained by DCE-MRI can be considered as a new approach to evaluate the tumor response after NAC [10]. However, all studies in this realm highlight the requirement of further improvements for a higher reproducibility of vessel analysis. This study proposed the application of a validated vessel extraction algorithm [15] as a standardized quantification tool for breast vessel quantification, overcoming limitations of the only existing vessel score system [7], based on human visual analysis. In particular, since vessels should pass a lower threshold in length and diameter, in order to be counted, Sardanelli system could categorize with the same score two breasts with the same number of vessels, but markedly different vessels extensions. The proposed method allows calculating the vascular volume per breast, therefore considering the real extension of vessels. Considering that the present study is still ongoing, preliminary results show evidence of a difference between responders and non-responders in the vessel volume reduction of cancer-bearing breast after NAC (median value of volume difference for responders = 1.71 cc; for non-responders = 0.41 cc;  $p = 0.003$ ), and therefore suggest a possible correlation between vessel volume reduction after NAC and pathologic tumor response.

The translation of the method into clinical practice was also considered. The radiologist established that the simultaneous visualization of AVMs during vascularity analysis allows

**Table 1 – Difference in volume, number of vessels and vascular score after neoadjuvant chemotherapy for vascularity evaluations with automatic vascular mapping (AVM) and without (no AVM), for responders (*resp*) and non-responders (*non-resp*). *p*-values were calculated using the two-sample Wilcoxon test; significant threshold was set at  $p < 0.05$ .**

	Volume (cc), median <sup>a</sup>			No. vessels, mean ± SD			Vascular score, mean ± SD		
	<i>resp</i>	<i>non-resp</i>	<i>p</i>	<i>resp</i>	<i>non-resp</i>	<i>p</i>	<i>resp</i>	<i>non-resp</i>	<i>p</i>
No AVM	–	–	–	2.0 ± 1.7	0.9 ± 1.5	0.14	0.8 ± 0.9	0.6 ± 0.9	0.90
AVM	1.71 (1.32–2.13)	0.41 (0.20–1.21)	0.003	2.5 ± 1.2	0.9 ± 1.7	0.03	1.5 ± 0.5	0.6 ± 1.0	0.02

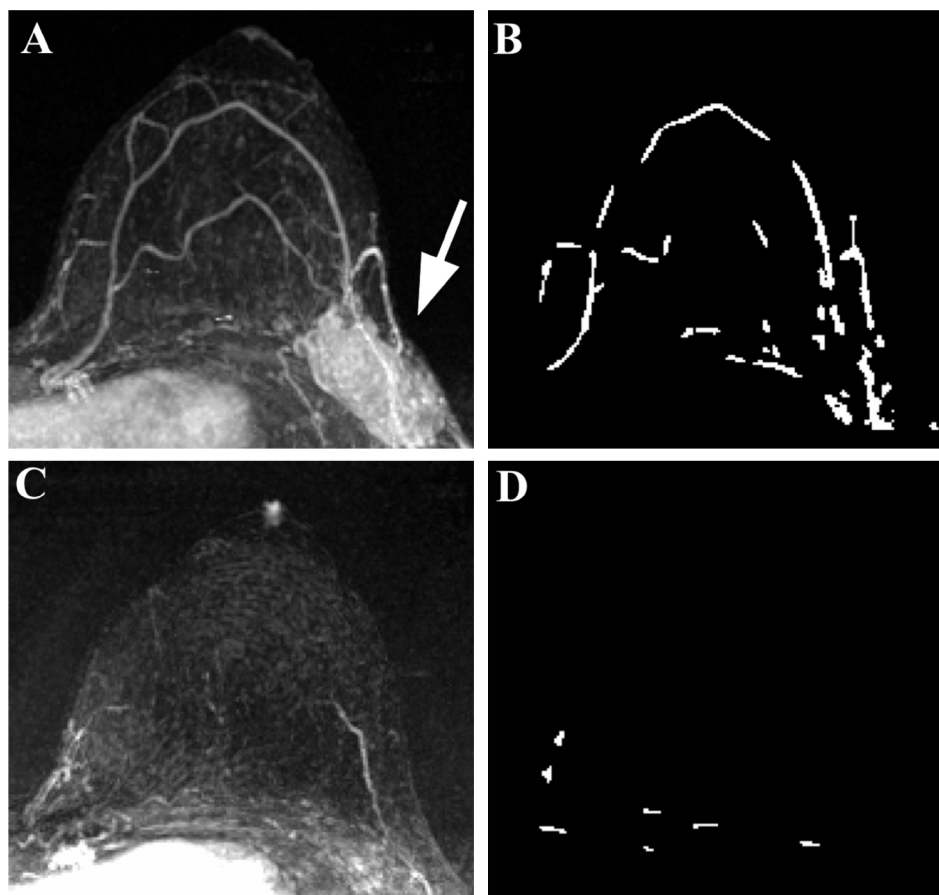
<sup>a</sup> Numbers in parentheses are interquartile ranges.

a more precise decision if the vessel should or should not be counted. The reduction of number of vessels and vascular score after NAC for breasts harboring the cancer showed a significant difference between responders and non-responders, when the evaluation was supported by the automatic mapping.

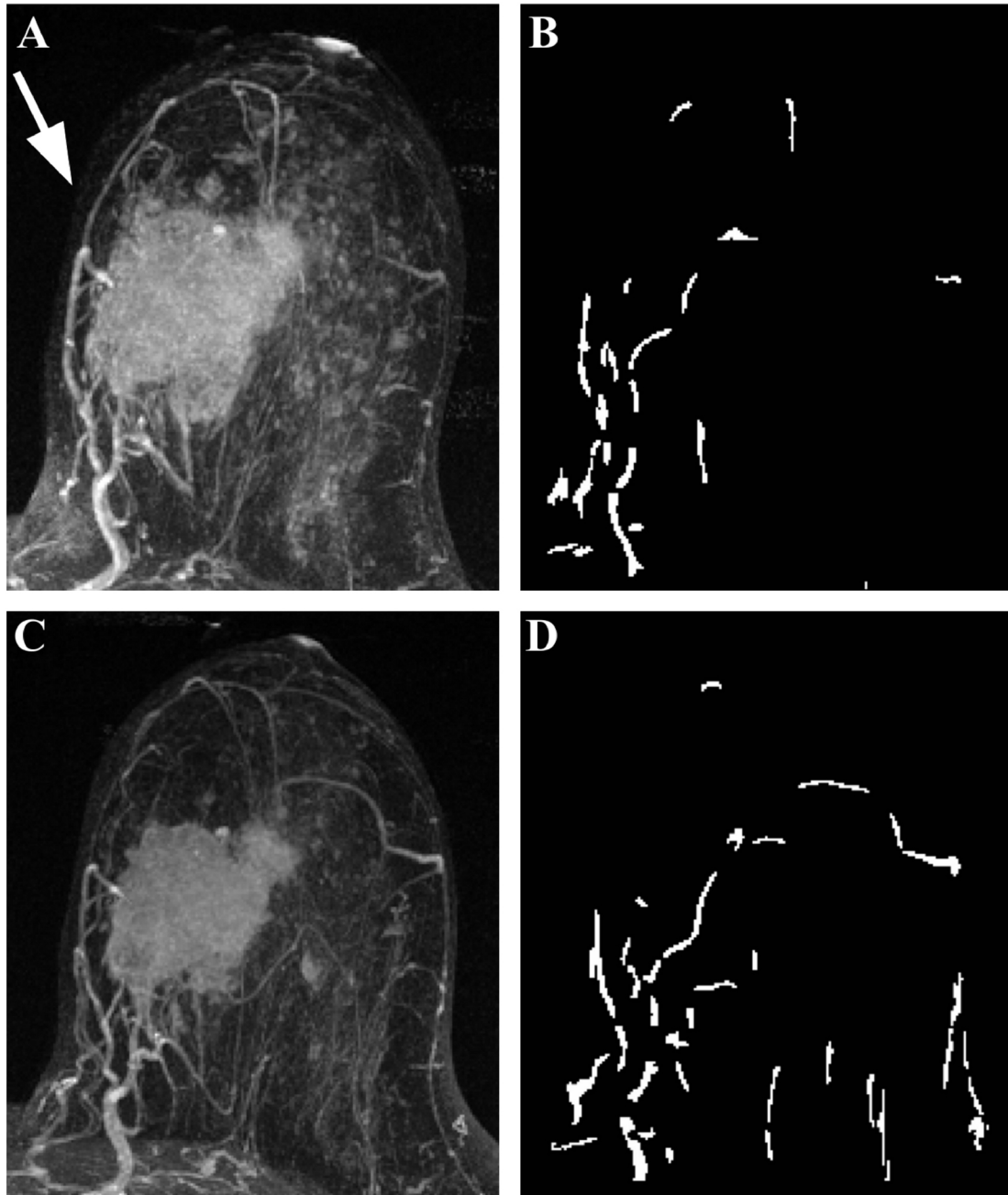
A few limitations of this study should be addressed. The dataset is limited, and results should be confirmed by a larger study. The automatic method still incorrectly detects some artifacts, and a proper improvement of the reduction of the number of non-vessel detected voxels should be considered. In order to represent a new biomarker for monitoring the response to neoadjuvant treatments in a clinical setting, a cut-off value in the vessel volume reduction should be defined,

able to reliably distinguish responders from non-responders patients. However, this was beyond the scope of the current retrospective study.

The evaluation of correlation of changes in vascularity with pathologic tumor response after NAC was proposed as an application of our previously published method to automatically extract breast vascular maps from DCE-MRI [15], but other purposes may be envisaged. In the era of targeted cancer therapy, in fact, there is a growing clinical interest in quantitative methods to evaluate the effects of anti-angiogenic drugs. Moreover, the extraction of AVMs may be integrated into Computer Aided Diagnosis (CAD) systems, aiming to reduce the labeling of vessels as suspicious regions, thus improving CAD specificity.



**Fig. 2 – A 29 years old woman with a locally advanced cancer (HER-2 Type Invasive Ductal Carcinoma) on the superior external quadrant of the left breast (pointed by arrow) and achieving pathologic complete response at the end of the treatment. Maximum Intensity Projection (MIP) of the subtracted image (A) and automatic vascular map (AVM) (B) before neoadjuvant chemotherapy (NAC), and MIP of the subtracted image (C) and AVM (D) after NAC.**



**Fig. 3** – A 45 years old woman with a locally advanced cancer (Luminal B Invasive Ductal Carcinoma) between the internal quadrants of the left breast (pointed by arrow) with stable disease after neoadjuvant chemotherapy (NAC). Maximum Intensity Projection (MIP) of the subtracted image (A) and automatic vascular map (AVM) (B) before NAC, and MIP of the subtracted image (C) and AVM (D) after NAC.

In conclusion, these encouraging results validate the use of an automatic multiscale 3D Hessian matrix-based algorithm for vessel detection in breast DCE-MRI. Moreover, these preliminary findings suggest the use of AVMs as new biomarker to evaluate the pathologic response after NAC, but AVMs may also find application in other breast DCE-MRI vessel analysis that are waiting for a reliable quantification method.

## 5. Conclusions

The application of a validated algorithm for automatic vessel extraction on DCE-MRI of the breast is proposed to support breast vascularity evaluation, recently investigated as a potential DCE-MRI descriptor correlated with cancer diagnosis and with the effect of NAC. In particular, the method provides a

standardized vascular mapping, its quantification based on vessel volume, overcoming the low reproducibility of current approaches based on human visual assessment. Taking into account the preliminary nature of the results here presented, the vessel volume difference of cancer-bearing breast after NAC demonstrated a correlation with pathologic tumor response.

### Conflict of interest statement

F.S. received research grants from and is on the speakers' bureau for Bracco Imaging Group and Bayer Pharma AG; L.M. was a blinded reader for Bayer Schering Pharma, was a speaker for Bracco Imaging Group. For the remaining authors, none were declared.

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