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Evaluating pathologic response of breast cancer to neoadjuvant chemotherapy with computer-extracted features from contrast-enhanced ultrasound videos

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ABSTRACT

Purpose: To extract quantitative perfusion and texture features with computer assistance from contrast-enhanced ultrasound (CEUS) videos of breast cancer before and after neoadjuvant chemotherapy (NAC), and to evaluate pathologic response to NAC with these features.
Methods: Forty-two CEUS videos with 140,484 images were acquired from 21 breast cancer patients pre- and post-NAC. Time-intensity curve (TIC) features were calculated including the difference between area under TIC within a tumor and that within a computer-detected reference region (AUT_T-R). Four texture features were extracted including Homogeneity and Contrast. All patients were identified as pathologic responders by Miller and Payne criteria. The features between pre- and post-treatment in these responders were statistically compared, and the discrimination between pre- and post-treatment cancers was assessed with a receiver operating characteristic (ROC) curve.
Results: Compared with the pre-treatment cancers, the post-treatment cancers had significantly lower Homogeneity ($p < 0.001$) and AUT_T-R ($p = 0.014$), as well as higher Contrast ($p < 0.001$), indicating the intratumoral contrast enhancement decreased and became more heterogeneous after NAC in responders. The combination of Homogeneity and AUT_T-R achieved an accuracy of 90.5% and area under ROC curve of 0.946 for discrimination between pre- and post-chemotherapy cancers without cross validation. The accuracy still reached as high as 85.7% under leave-one-out cross validation.
Conclusions: The computer-extracted CEUS features show reduced and more heterogeneous neovascularization of cancer after NAC. The features achieve high accuracy for discriminating between pre- and post-chemotherapy cancers in responders and thus are potentially valuable for tumor response evaluation in clinical practice.

1. Introduction

Neoadjuvant chemotherapy (NAC) is given to patients with locally advanced breast cancer in order to downstage the primary tumor and to reduce or eliminate micrometastatic disease [1–3]. Accurate evaluation of cancer response to NAC is critical for making optimal treatment decisions. Magnetic resonance imaging (MRI) and mammography have been used in the response evaluation of breast cancer [2–5]. However, they suffer from a long examination time, ionization, immobility, or high cost. In contrast, due to its advantages of non-ionization, fast and real-time imaging, flexibility and mobility, and low cost, the contrast-enhanced ultrasound (CEUS) has gained increasing attention in response evaluation of breast tumor [6].

CEUS involves intravenous administration of contrast agents containing microbubbles for real-time visualization of microvessel perfusion in tumor, which manifests the tumor neovascularization that may be an important factor for evaluating the effects of NAC [6–8]. However, visual interpretation of the CEUS videos is subjective, tedious and time-consuming for a radiologist or oncologist, which also limits the accuracy of response evaluation. Therefore, researchers have been devoted to developing computer-assisted quantitative approaches for more accurately, objectively and efficiently interpreting and comparing CEUS videos of breast cancer before and after NAC [6].

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A CEUS video often lasts for a few minutes and may include thousands of sequential images. Time-intensity curve (TIC) analysis is a state-of-the-art technique for CEUS video quantification, which extracts quantitative parameters of blood perfusion in a lesion [6–8]. As well as the parameters obtained within the lesion, the ratios or differences of the parameters within the lesion and those within a background reference region (e.g., a normal tissue [9] or an artery lumen [10]) are sometimes also calculated as new parameters, which have been normalized by using the reference region and may be more accurate in lesion characterization. To our knowledge, however, the CEUS parameters of ratios and differences have never been employed in tumor response evaluation. Thus it is still unclear whether the reference region should be used and where it should be objectively placed.

Moreover, the TIC analysis only calculates the variations of perfusion intensity over *time*. It would be desirable to quantify the perfusion variations over *space* too, i.e., the spatial heterogeneity of perfusion [10]. The texture analysis offers a promising technique for quantifying tissue heterogeneity, and it has recently been adopted in MRI, multiparametric ultrasound (US), and computed tomography for measuring tumor heterogeneity [4,11–13]. However, the role of texture analysis on CEUS images for tumor response evaluation is yet to be determined.

The aim of this study was to investigate the effectiveness of computer-assisted quantification on CEUS for evaluating the pathologic response to NAC by measuring blood perfusion with a computer-detected reference region and quantifying cancer heterogeneity with texture analysis.

2. Materials and methods

2.1. A CEUS image dataset of breast cancer

This retrospective study was approved by our institutional review board and the requirement for informed consent was waived. We retrospectively identified patients undergoing breast surgery following NAC. Twenty-one women (mean age, 45.7 years; range, 28–63 years) were included according to the following criteria: (i) patients had biopsy-proven breast cancer before NAC; (ii) patients underwent at least four cycles of NAC; (iii) CEUS videos were available both before and after NAC; (iv) patients underwent either modified radical mastectomy or breast conserving surgery following NAC; (v) a histopathological examination report was available for the surgical specimen after NAC.

The chemotherapeutic drugs were administered intravenously every three weeks for one NAC cycle. The NAC was performed until the primary inoperable tumors became operable or the primary operable tumors became suitable for the breast conserving surgery. Before and after NAC, all patients underwent both conventional US and CEUS examinations with the MyLab 90 system (Esaote SpA, Genoa, Italy). All conventional US and CEUS examinations were performed by a radiologist with 20 years of experience in breast US. The largest imaging plane of a tumor or the plane with the richest blood supply was selected for CEUS before NAC, which included both the tumor and its surrounding normal tissues and most vividly manifested tumor's perfusion characteristics. The plane after NAC was selected in order to be consistent with the pre-NAC plane according to the recorded pre-NAC location of the tumor. The CEUS imaging was carried out with a 4–13 MHz linear transducer (LA522) and a bolus injection of 2.4 mL of the contrast agent SonoVue (Bracco SpA, Milan, Italy). During CEUS imaging, the selected plane remained unchanged and the real-time video images were continuously recorded for about 3 min. Hence a dataset of 42 videos (140,484 images) with each video containing 3345 ± 776 images was acquired for further computer-assisted image interpretation and analysis.

2.2. Time-intensity curve analysis with a computer-detected reference region

Semi-automatic software was written in-house with MATLAB R2014a (MathWorks, Natick, MA, USA) and employed to conduct the TIC analysis, which consisted of the following steps.

2.2.1. Tumor and intratumoral bright region detection

A motion compensation algorithm using the normalized cross-correlation [10,14] was used to correct the respiratory movement of the breast tumor. A tumor region of interest (ROI) was manually drawn to outline the tumor along its border. The TIC of the tumor ROI was generated and smoothed to identify the peak frame, from which an intratumoral bright ROI was then automatically detected within the tumor ROI by using an adaptive thresholding method proposed in our previous study [15]. The tumor ROI was thus segmented into two regions, one with bright intensities and the other with dark intensities; the bright region denoted the area with US contrast enhancement and thus presumably represented the intratumoral neovascularization. For details of the ROI detection, please refer to our previous work [10,15].

2.2.2. Reference region detection

We proposed an algorithm to automatically detect a reference region in the surrounding normal tissues of a breast tumor. The reference region should be located in normal tissues and meet the following criteria: outside the tumor; at the same depth of the tumor; not in the fascia; and with homogeneous contrast enhancement. Our algorithm was proposed to conform to these criteria.

The reference region detection was first limited to a rectangular region at the same depth of the tumor (magenta dashed rectangles in Fig. 1). The tumor border (r_i, θ_i) was then expanded by a distance of r_e = 0.5 cm at the polar coordinates, and only the region outside the expanded border (r_i', θ_i') was used as the candidate area for the reference region:

$$\begin{cases} r_i' = r_i + r_e \\ \theta_i' = \theta_i \end{cases} \quad (1)$$

where r_i and θ_i denoted the distance and orientation of the i-th discrete border point to the tumor center that served as the origin of the polar coordinates. Here, the use of 0.5 cm expansion has been inspired by the safe margin of resection used in cancer surgery, when surgeons resect the cancer along with a rim of seemingly normal tissue to ensure that all cancer cells have been eliminated.

Subsequently, the adaptive thresholding [15] was employed at the entire image of the peak frame after the mean filtering so as to detect the brightest contrast-enhanced region, which was considered as the fascia and thus excluded from the candidate area. Only a few pixels remained in the candidate area (white area in Fig. 1b and d), and the pixel with the largest intensity was selected as the center of the reference region. Finally, the reference region with a diameter of 0.2 cm was determined automatically and objectively (red circles in Fig. 1). The size of 0.2 cm was set to ensure the contrast enhancement within the reference region was homogeneous.

2.2.3. TIC feature extraction

For each CEUS video, TIC parameters were calculated from three ROIs (i.e., the tumor, intratumoral bright region, and reference region), and their ratios and differences are derived as new parameters. From one ROI, two TIC parameters were extracted consisting of the area under the TIC (AUT) and mean transit time (MTT) [6,10,16]. For clear descriptions, the TIC parameters were named with a postfix of "T" denoting the tumor ROI, "B" denoting the

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