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Ultrasound scattering statistics predicts the result of neoadjuvant chemotherapy of breast tumors at an early stage of treatment

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***Abstract*—Neoadjuvant therapy (NAC) for breast tumors involves administering chemotherapeutic agents to the patient before a tumor resection surgery. An assessment of a cancer response to the medicine is an important aspect of the therapy. It is necessary to decide whether to continue the treatment, change the drug or refer the patient to a surgery to remove the tumor. Quantitative Ultrasound (QUS) techniques can help in assessing the therapy and the decision-making process. These techniques provide quantitative parameters related to a tissue structure, thus changes in the parameters values can be related to changes in the tissue. The aim of this study was to assess the tumor response to the therapy, basing on statistical parameters of backscattered ultrasound signals. The data were acquired from 34 tumors during NAC therapy. First measurement (a baseline) took place before a start of the therapy, and next measurements were carried out about a week after each NAC administration. At the end of the treatment, the tumors were excised, examined histopathologically, and a percentage of residual malignant cells (RMC) in tumor tissue was estimated. As a part of the data analysis, an experienced physician specified a tumor area (Region of Interest - ROI) on each ultrasound image. Then, two statistical parameters of a signal amplitude probability distribution within the ROI was estimated. The first was the shape parameter of the homodyned k distribution, and the second was the Kullback-Leibler divergence between amplitude distributions estimated from the baseline and succesive masurements. These parameters were used to classify tumors during therapy as "responding" or "not responding" to treatment, assuming that non-responding tumors have an RMC $> 75\%$. Results suggest that QUS parameters obtained from amplitude statistics can be useful in the NAC monitoring and provide additional information to physicians**

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***Index Terms*—Quantitative ultrasound, neoadjuvant chemotherapy, cancer response monitoring**

I. Introduction

Women breast cancer is one of the most commonly diagnosed cancer and one of the leading causes of cancer-related deaths [1]. Neoadjuvant chemotherapy (NAC) is used in breast cancer patients to reduce tumor size, decrease the risk of local recurrence, and diminish the likelihood of metastases. Monitoring NAC effects is necessary in clinical decisions, for example to capture resistant patients and stop or change the treatment. In general the monitoring is often based on tracking the tumor size changes during the therapy. A clinical breast examination (CBE), and imaging techniques like mammography (MMG), traditional ultrasound imaging in B-mode (US), or magnetic resonance imaging (MRI) can be used for monitoring. The MRI is the most accurate, however, it is a technique with limited availability. The classical US is considered a more accurate method in assessing the tumor size than CBE or MMG [2]. It also has been shown that a decrease in tumor stiffness is a good predictor of the pathological response [3]. However, methods based on monitoring changes in the tumor size have numerous limitations [2]. Such changes occur with a delay compared to changes in the tumor microstructure. Besides, sometimes there is no apparent reduction in a tumor size, although the pathological response to the treatment is positive.

An interesting alternative to the approach based on tracking changes in the tumor during the therapy is the use of quantita-

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tive ultrasound (QUS) methods. The QUS techniques are based on an estimation of some tissue characterizing quantitative parameters from raw, ultrasonic radio-frequency echoes (RF). It was shown that QUS parameters are important biomarkers of NAC therapy. Lin et al. used animal models of breast cancer to show that the spectral analysis of ultrasonic echoes provides a way to assess the tumor response to chemotherapy [4]. Sannachi et al. have shown that after the fourth week of treatment the use of a combination of the average scatterer diameter and the average acoustic concentration allows for the differentiation of responding and non-responding patients, with a sensitivity of $82\,\%$ and a specificity of $100\,\%$ [5]. In another study Sadeghi-Naini et al. used QUS methods which were able to predict the outcome of chemotherapy in patients with breast cancer with the AUC (area under the receiver-operating characteristic curve) of 0.80 and 0.89, respectively, 4 and 8 weeks after the start of the treatment [6].

The purpose of this study was to evaluate the performance of the NAC monitoring using QUS parameters based on changes in backscatter amplitude distribution. In the study the shape parameter of the homodyned K distribution (HKD) and the Kullback–Leibler divergence (KLD) were used.

II. Methods

A. Data acquisition

Tumors undergoing neoadjuvant chemotherapy were examined as follows. The first ultrasound examination of each tumor (a baseline) was carried out before the start of the therapy. Further examinations were conducted a week after each drug administration. The time interval between drug administrations was 3 weeks and the whole therapy for each patient lasted 4–5 months. All tumors were invasive carcinomas of no special type (NST). The number of examined tumors was equal to 34. The average age of patients and average tumor volume was equal to 55 and $8\,\mathrm{cm}^3$ respectively. Each tumor was imaged in four planes: radial, radial$+45°$, anti-radial and anti-radial$+45°$. All examinations, including tumor boundary determination, were performed by an experienced sonographer. The study protocol was approved by the institutional review board of the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland. All procedures performed in the study that involved human participants were in accordance with the guidelines set by the 1964 WMA Declaration of Helsinki and its later amendments or comparable ethical standards. All patients gave written consent to participate in the study.

The ultrasound RF data were acquired using an ultrasound scanner (Ultrasonix SonixTouch-Research, Ultrasonix Medical Corporation, Richmond, BC, Canada). The scanner was equipped with a research module capable to record raw radio-frequency data (RF). The data were acquired using the linear probe (L14-5/38), and the transmitted pulse frequency was set at $10\,\mathrm{MHz}$. RF images were collected from each cross-section, and the rest of processing was performed off-line using Matlab® 2017a (The MathWorks, Inc., Natick, Massachusetts, United States).

After the last course of NAC each tumor was excised and a histopathological analysis was carried out. The pathologist specified the percentage of residual malignant cells (RMC), which described how many cancer cells were within the removed tumor. It was assumed that the parameter RMC represents the degree of tumor resistance to therapy. The minimal value ($0\,\%$) of the RMC parameter corresponded to a complete pathological response to NAC, i.e. no residual malignant cells were found in the test sample. The maximum number ($100\,\%$) corresponded to lack of response i.e. the whole sample was occupied by undamaged cancer cells, which means that the therapy was completely ineffective.

B. Quantitative parameters

Two quantitative parameters were determined based on the acquired ultrasound data. The first parameter was a shape parameter μ of the homodyned K distribution (HKD) [7], [8]. The probability density function (PDF) of the homodyned K distribution is given by (1):

$$p(A) = A \int_0^\infty x J_0(sx) J_0(Ax) \left(1 + \frac{x^2\sigma^2}{2\mu}\right) dx \qquad (1)$$

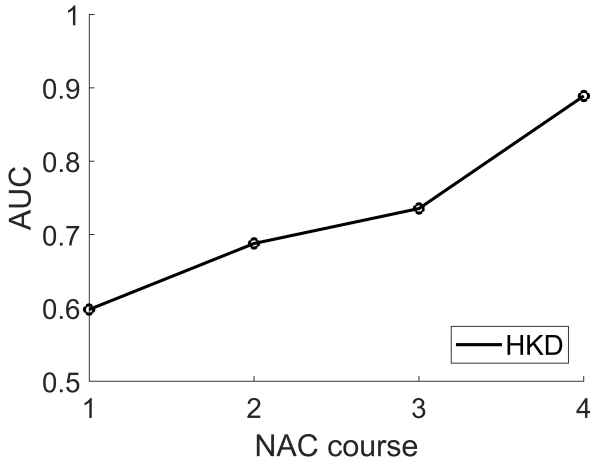
where A is an amplitude, J_0 is the zero order Bessel function of the first kind, and s^2 and σ^2 represent the coherent and diffuse signal energy respectively. The parameter μ is related to the effective number of scattering elements in the resolution cell and was estimated using the method proposed by Hruska and Oelze [9]. The second parameter was the Kullback-Leibler divergence (KLD) [10]. The KLD is a measure of a difference between two probability distributions P and Q, and is given by (2):

$$KLD(P||Q) = \int_{-\infty}^{\infty} P(x) \log\left(\frac{P(x)}{Q(x)}\right) dx \qquad (2)$$

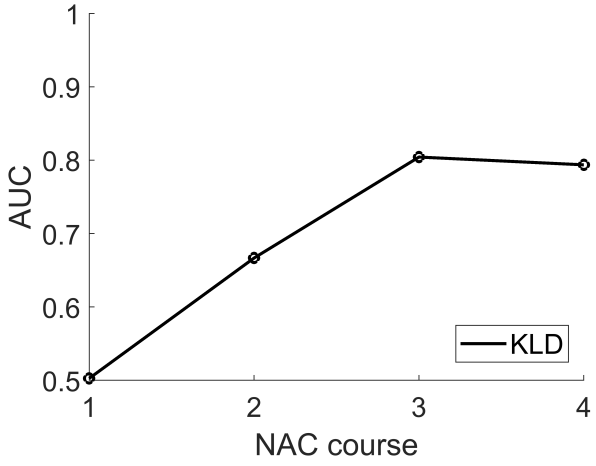
The P distribution was determined based on the data obtained before the treatment, while Q was related to the data collected after each subsequent round of the chemotherapy. In this study it was assumed that RMC higher than $75\,\%$ corresponds to an ineffective therapy. Both parameters were tested as classifiers to check if they could be used to predict the final effectiveness of NAC, by classifying the tumor into 'responding' or 'non-responding' class. The classifiers were cross-validated using the 'leave-one-out' method [11]. For both classifiers the Receiver Operating Characteristic (ROC) curve [12], as well as the Area Under the ROC Curve (AUC) were estimated. The AUC values were used to assess the efficiency of the classification.

III. Results and discussion

The AUC was used to assess QUS parameters for capturing non-responding tumors, assuming an RMC value $>75\,\%$) for resistant cases. The results are presented in Fig. 1. The effectiveness of the classification using each of the examined QUS parameters increases with successive NAC courses. The HKD AUC reached 0.90 after the fourth drug administration. In turn, the KLD AUC reached 0.80 after the third drug administration.



(a)



(b)

Fig. 1. The AUC values determined after succesive doses of NAC for classification by HKD (a) and KLD (b) assuming that cases not responding to treatment have RMC $> 75\,\%$.

The increase in efficiency with subsequent NAC courses is most likely associated with increasing microstructural differences between responding and non-responding tumors. In responding tumors, cancer cells nuclei are defragmented during the therapy, and the microstructure is reorganized [13]. Such changes occur gradually over the course of the therapy, and affect statistical characteristics of the backscatter.

IV. CONCLUSIONS

Classifiers based on a single statistical parameter have shown promising results in monitoring NAC therapy after the third (KLD) and fourth (HKD) dose of the drug. These results suggest the potential utility of statistical ultrasound markers in monitoring tumor response during NAC treatment. The research will be continued to verify if it is possible to significantly increase the classification efficiency by creating classifiers that use more parameters, not necessary basing on statistics of backscatter only.

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