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Quantitative ultrasonography as a tool for the evaluation of breast tumor response to neoadjuvant chemotherapy

Hanna Piotrzkowska-Wróblewska[1], Katarzyna Dobruch-Sobczak[2], Jerzy Litniewski[1]

[1] *Department of Ultrasound, Institute of Fundamental Technological Research Polish Academy of Sciences, Warsaw, Poland*
[2] *Radiology Department II, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Correspondence: Hanna Piotrzkowska-Wróblewska, Department of Ultrasound, Institute of Fundamental Technological Research Polish Academy of Sciences, Pawinskiego 5B, 02-106 Warsaw, Poland; e-mail: hpiotrzkowska@gmail.com

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Abstract

Neoadjuvant chemotherapy is increasingly becoming the first treatment step in breast cancer. Despite the enormous advantages of this therapy, it is a method characterized by a high level of toxicity and thus carries a huge burden for the patient. Therefore, it is highly desirable to begin monitoring the patient's response to treatment at an earlier stage. Currently, apart from traditional imaging methods, a completely new technique (in the context of monitoring the outcomes of chemotherapy), called quantitative ultrasound, is gaining popularity. It is a method based on the exact same ultrasound echoes as in traditional ultrasound imaging. The innovative approach of the method is that these echoes are not used for visualization but to characterize the condition of the tissue by parameterizing it with the aid of ultrasound biomarkers. The biomarkers make it possible to assess the state of the tissue at the microscopic level, and thus evaluate changes occurring in the tissue under the influence of treatment at a very early treatment stage. The present paper aims to familiarize the reader with the physical foundations of this method as well as present the latest results of related research.

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide. In 2018, there were 562,500 new cases in the world, including the European Union countries. This places breast cancer first among other cancers in terms of the frequency of occurrence in women, accounting for 25.1% of all cancers[1].

According to the GLOBCAN report, the number of new cancer cases in the world in the coming years will exhibit an upward trend. Forecasts indicate that in 2024 the number will exceed 3 million[2]. A rising trend in the number of cancer cases can also be observed in Poland; however, it is not accompanied by an increase in the mortality rate. This effect is most likely the result of the impact of screening tests and increasingly modern therapeutic methods[3]. Specifically, data provided by experts from Australia, Germany, Italy, the United Kingdom, and the United States showed that, in a group of patients diagnosed with breast cancer, 7–27% were treated with neoadjuvant chemotherapy (NAC)[4]. This therapy includes treatment before surgery, specifically consisting of cyclical administration of chemotherapeutic agents in order to reduce the size of the tumor, lower the risk of local recurrence and distant metastases and, consequently, achieve better clinical outcomes. Taking into account the latest recommendations regarding the application of NAC, it should be expected that the number of patient referred for NAC will increase.

Currently, the most reliable method of determining the efficacy of NAC treatment is the assessment of the pathological response of tumor, which consists of the histopathological analysis of postoperative material. The lesion size, cellularity, histological type, in situ component, surgical margins, and degree of histological malignancy are also assessed. The material examined during this assessment is the tumor that has been treated (marked with a marker before

treatment is started) or, in the case of complete regression, the tissues surrounding the marker.

However, the assessment is performed at the end of treatment. During therapy, which takes place over many weeks, changes occurring at the tumor cellular level are not subjected to histopathological verification, except for clinical tests.

The remaining diagnostic methods and the assessment of clinical response are mainly based on the monitoring of tumor dimensions. According to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), the type of tumor response is determined by comparing the longest diameter of the lesion upon pre-treatment and during-treatment examination[5]. Despite different imaging techniques used to monitor patients undergoing NAC, no unambiguous standards have been published thus far. Currently, mammography (MMG), ultrasoud (US) imaging, and, in some patients, magnetic resonance imaging (MRI), are used as techniques for assessing tumor size before, during, and after chemotherapy[6].

MMG, in the context of assessing the presence of residual tumor after treatment, is characterized by low specificity due to the frequent underestimation of the rate of response to treatment. Insufficient measurement accuracy is often related to parenchymal distortion; the presence of spicules; and difficulties in identifying the border of the lesion, which may be masked by normal tissue, especially in patients with aglandular breast structure. Additional drawbacks include the monitoring of the presence of microcalcifications, which do not correlate with tumor response to treatment. US imaging is characterized by a higher sensitivity compared to that of MMG[6]. The assessment of lesion size on the basis of the US image is, however, subjective in nature, largely dependent on the operator[7–8].

Other advanced methods that do not only rely on changes in tumor dimensions as a criterion for response to treatment but instead analyze physiological alterations and changes at the molecular level include functional MRI imaging, diffusion MRI imaging, proton MRI spectroscopy, fluorodeoxyglucose-positron emission tomography (FDG-PET), fluorothymidine-positron emission tomography (FLT-PET), and choline C-11-PET[9,10]. However, these methods cannot be adapted to evaluate the efficacy of response to NAC in everyday clinical practice. Apart from the high cost of these techniques, they also require the administration of a contrast agent and/or the use of ionizing radiation.

However, there is a method based on the use of quantitative ultrasound (QUS) that can fill the gap between histopathological examinations and imaging.

This method has the advantages of modern US imaging (e.g., non-invasiveness, safety, and low examination costs) but can also characterize the state of the tissue microstructure using quantitative parameters (i.e., biomarkers) determined by the analysis of raw US echoes. Ultrasonic echoes (also called raw radio frequency [RF] signals) are the same ultrasonic echoes on which modern US imaging is based. Today, most major clinical ultrasound manufacturers can provide RF access in addition to clinical imaging packages. However, research contracts may still be required to gain RF access.

This paper aims to familiarize the reader with both the physical basics of QUS and the results of research published at both preclinical and clinical research stages.

Basic information on quantitative ultrasound in the context of monitoring changes in breast tumors during NAC treatment

The RF ultrasonic echo, received by the transducer at the moment of examination, is the sum of many echoes originating from microstructures (scatterers) located in the measuring volume (defined by the beam width and length of the transmitted ultrasonic pulse)[11]. Depending on the physical and material properties as well as the spatial distribution of the scatterers interacting with the propagating wave, it is characterized by a specific amplitude and phase (Fig. 1).

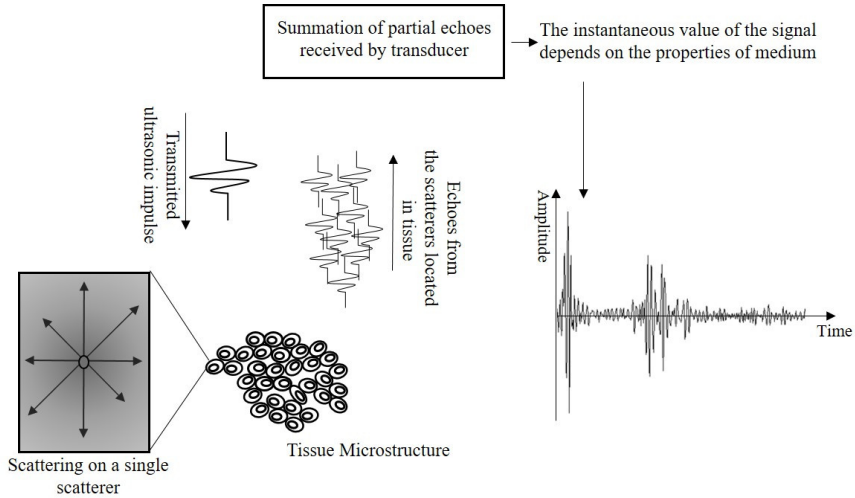

Fig. 1. *Diagram of ultrasonic RF signal formation as a result of scattering on inhomogeneities present in the tissue*

Tab. 1. *Characteristics of the ultrasonic parameters discussed in the article*

Determination method	Parameter name and definition	Tissue features affecting its value
Spectral parameters – determined directly from the signal spectrum in the frequency range corresponding to the transducer frequency band	Mid-band fit (MBF) [dB]	Size, shape, quantity, and elastic properties of scatterers
	0-MHz intercept (SI) [dB]:	Size, shape, quantity, and elastic properties of scatterers
	Spectral slope (SS) [dB/MHz]:	Size, shape of scatterers
Backscatter scattering parameters – determined on the basis of the backscattering coefficient in the frequency range corresponding to the transducer frequency band	Average scatterer diameter (ASD) [μm]	Average size of the scatterers (e.g., single cells or clusters of cells)
	Average acoustic concentration (AAC) [dB/cm^3]	Spatial density, organization, elastic properties of scatterers
	Integrated backscatter coefficient (IBC) [dB]	Size (AND), shape, quantity, organization, and elastic properties of scatterers
Statistical properties		
First-order statistical properties of the RF echo envelope – basic concept relies on modeling the magnitude of speckle with probability density functions, shape parameters of the K homodyne distribution	ENS – effective numbers of scatterers the scatterer clustering parameter	Quantity, organization, and elastic properties of scatterers
	k – the structure parameter	Size, elastic properties of diffusing structures

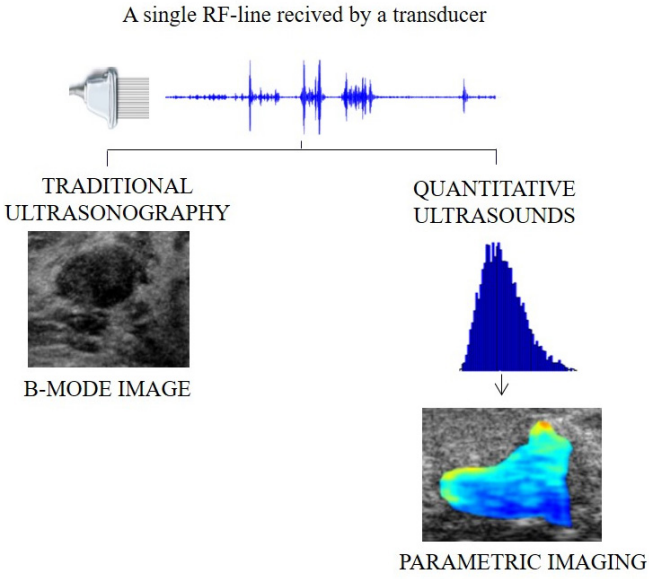

Fig. 2. *Principle of operation of traditional ultrasonography (B-mode imaging) and quantitative ultrasound. In the case of a parametric map (generated based on the analyzed biomarker value – the effective number of diffusers), red denotes high values of the parameter (indicating a large number of identical small scatter structures), while blue represents low values (indicating a small number of large scatterers, e.g., clusters of cancer cells)*

In the case of breast tumors, microstructures interacting with the propagating wave at a central frequency of 10 MHz (the typical frequency used in clinical studies of the breast) can be understood as tumor cell clusters, stroma fragments, adipocytes, micro- and macrocalcifications, and blood morphotic elements[12,13]. As a result of NAC therapy, in the case of tumor response to treatment, the microstructure of the malignant lesion is remodeled (i.e., the microstructures that interact with the US wave are also modified)[14]. Commonly used US scanners, which generate a traditional B-mode image of the examined organ, consider the envelope of RF signals, which is post-processed to obtain the best image quality. Although these images can show some qualitative and quantitative information, most of the information on the microstructure of the tissue is lost. QUS makes it possible to use all information contained in the RF signal[15]. Through the quantitative analysis of RF signals based on, e.g. spectral analysis or evaluation of the statistical properties of the signal envelope, the state of the tissue is characterized by a number of QUS biomarkers[16]. Some of them are listed in Tab. 1. The underlying principle of QUS is illustrated in Fig. 2.

In classic imaging, only filtration is used to obtain the best image quality. The quantitative assessment is based on a more advanced analysis of the RF signals, with the aim of extracting as much information as possible in the form of quantitative parameters to characterize the microstructure of the tissue.

Results of studies using QUS to evaluate the efficacy of NAC in patients with breast cancer

US parameters that enable the monitoring of tissue properties under the influence of NAC may be related to both the physical properties and microstructure of the medium (e.g., the examined tissue). The most commonly used method involves evaluating the condition of the tissue based on the use of scattering properties. US scattering is a fundamental phenomenon that occurs when a wave interacts with the tissue microstructure. The shape of the frequency spectrum, the backscattered signal, is related to the shape, size, and elastic properties of the scattering medium (e.g., frequency dependencies), and its amplitude with the shape, density (e.g., quantity of scatterers in the measuring volume), and scattering force of the scatters (e.g., the difference in acoustic impedance between the scatterers and the deferring medium). By analyzing the spectrum of the RF signal, it is possible to determine the number of US biomarkers, such as the integrated scattering coefficient (IBC), spectral

slope (SS), spectral intersection (SI) at 0 MHz, middle band (MBF), mean diameter of the spreader (ASD), average acoustic concentration (AAC), and spacing between the scatterers (SAS). The parameters are related to specific tissue characteristics, such as the AAC number and spatial density of the scatterers, the SI organization of the scatterers, and the SAS distances between the scatterers. Structures dispersing in neoplastic tissue refer, for example, to the elements of stroma or clusters of cells[17,18].

The first results of a pilot study on the use of spectral analysis in the assessment of the efficacy of NAC in women with breast cancer were presented in 2013 by Czarnota's team from the Sunnybrook Health Sciences Center in Toronto. This pioneering research was conducted on a small group of patients ($n = 24$) with locally advanced breast cancer. US data was recorded before treatment initiation and four times during treatment (1, 4, and 8 weeks after treatment initiation and before surgery). The authors showed that, in using the average values of parameters, such as the mid-band fit (MBF), slope (SS), and spectral crossover (SI), it was possible to distinguish a group of patients not responding to treatment. Moreover, the study exhibited a sensitivity of 100% and specificity of 83.3% within four weeks after treatment initiation[19].

A year later, the same research group used the other three scattering parameters (i.e., IBC, ASD and AAC) with the aim to predict NAC's results. Based on the same measurement scheme as in their previous study, in a group of 30 patients, they showed the AAC parameter to be a biomarker enabling the identification of patients responding to NAC as soon as one week after the start of treatment. It was also found that the IBC values increased throughout therapy only in the group of responding patients; in the absence of any tumor response, the IBC remained constant. Using the multi-parameter approach, the authors demonstrated that it was possible to predict the response to treatment with a very high sensitivity and specificity (82% and 100%, respectively) after four weeks of treatment[20].

To evaluate the effectiveness of NAC, the above-mentioned pilot studies used the mean values of biomarkers determined for the entire mass of the tumor. The analysis of tumor changes due to chemotherapy may suggest that this is not always the best method[21]. Mean values represent global changes that may mask subtle remodeling of the tissue microstructure, especially at the beginning of therapy. Generating and analyzing the previously mentioned parametric maps seems to represent a solution that can provide more accurate information. Textural parameters such as, for instance, homogeneity, variance, contrast, and correlation, which quantify the spatial relationship between local acoustic properties within tissue microstructures, are capable of characterizing the heterogeneous response within a tumor, particularly early on in the treatment process.

Such an approach was presented by Tadayyon *et al*. (2014). The authors showed that the mechanisms of cell death induced by chemotherapy within the tumor elicited morphological changes in the tumor cells, causing measurable changes in tissue echogenicity. The changes taking place at an early stage are reflected in changes in the textural characteristics of the spectral parametric ultrasonic maps. As demonstrated by Tadayyon *et al*., the simultaneous use of parameters characterizing the texture of the spectral parametric maps along with changes in their mean values allowed for predicting the final response of patients with breast cancer to chemotherapy with a sensitivity of up to 100% and specificity of 93% ($p = 0.002$)[22].

In addition to the spectral analysis of RF signals, there are also QUS methods based on the statistical analysis of the envelope of the backscattered signal. The key issue in the context of modeling the statistics of the envelope of the signal recorded from the medium featuring changes in the number and characteristics of the scatterers is the selection of the probability density distribution function. One type of probability density function with a wide range of possible applications is called K homodyne distribution. This density function does not require assumptions regarding the number or spatial distribution of diffusers. Specifically, the distribution is characterized by two quantitative parameters that can be related to the microstructure of the tissue: one is the effective number of scatterers (ENS), a parameter whose size is related to the actual number of scattering structures and the parameter modeling of their real contribution (e.g., efficiency) to the echo of the signal, and the other is (k), a parameter describing the ratio of the coherent signal to the scattered signal. The value of this parameter is equal to 0 in the absence of a coherent component (i.e., no reflections)[23,24]. Analyzing the tissue microstructure, it can be concluded that the lack of a coherent component corresponds to the lack of large (in terms of the wavelength) scattering structures (e.g., microcalcifications).

Statistical analysis using ENS as a parameter differentiating patients responding and not responding to NAC treatment was carried out on a group of 34 cancerous lesions by Klimonda *et al*.[25]. US data from the patients participating in the studies was recorded before the start of treatment and one week after each administration of the chemotherapeutic agent. On average, the tumors were subjected to five cycles of chemotherapy. The authors showed that classifiers based on only one statistical parameter had a great potential as predictors of responses to NAC. Based solely on ENS, it was shown that it was possible to differentiate between responders and non-responders, with the most accurate prediction in the study occurring after the fourth course of NAC treatment (after course I, AUC = 0.6; after course II, AUC = 0.7; after III, AUC = 0.75; after IV, AUC = 0.9).

Tissue remodeling at various stages of treatment is a complex process, featuring changes in both the neoplastic cells and in the stroma. In the case of changes within cells, one can consider both changes in the cellular organization of the tumor (e.g., dissociation, discohesion) and changes related to the death of cancer cells (e.g., nuclear and cytoplasmic vacuolization, pyknosis, karyolysis). These changes are usually accompanied by a stromal response that includes fibrosis, elastosis, collagenization, and infiltration

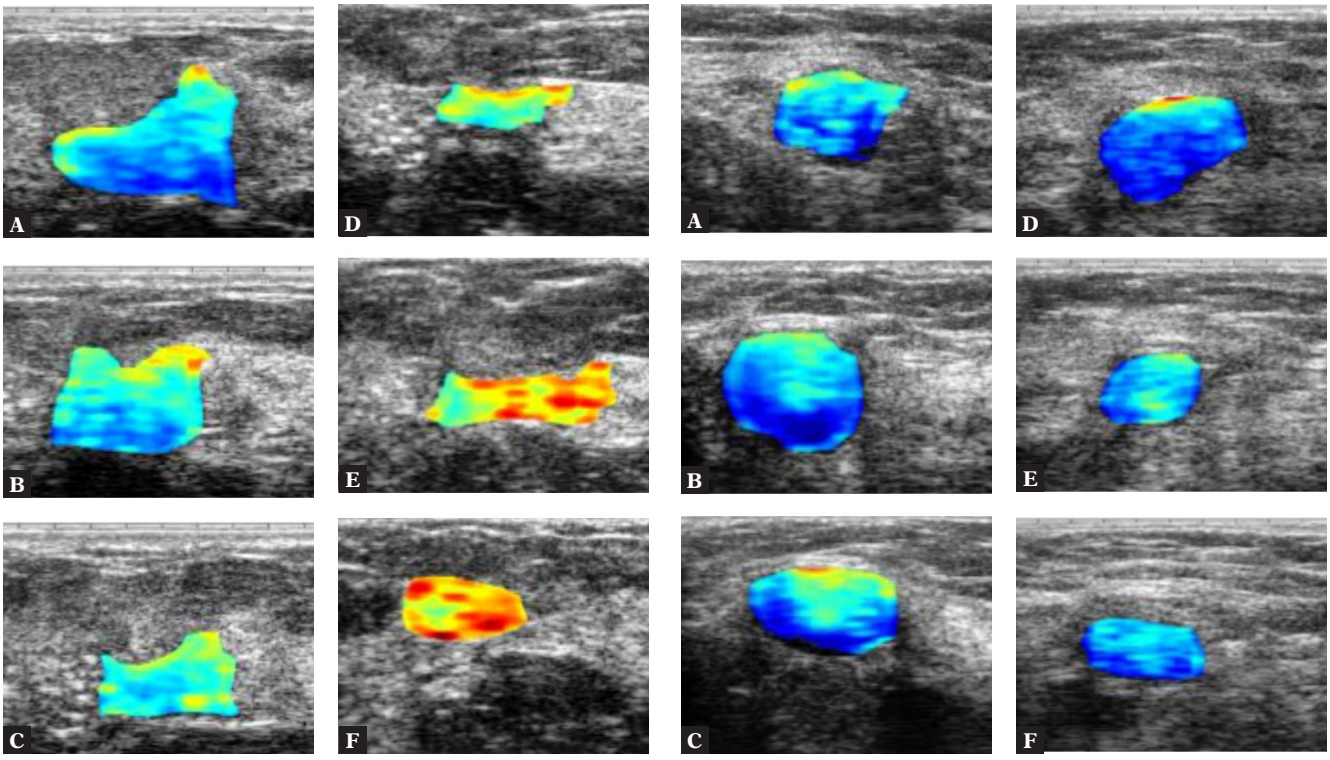

Fig. 3. *B-mode ultrasound images with overlaid parametric IBC images determined for a patient responding to NAC before (***A***) and one week after each chemotherapy cycle (***B–F***). Blue indicates low IBC values; red indicates high values*

Fig. 4. *B-mode ultrasound images with overlaid parametric IBC images determined for a non-responder to NAC before (***A***) and one week after each chemotherapy cycle (***B–F***). Blue indicates low IBSC values; red indicates high values*

by lymphocytes, plasma cells, and fibroblasts[26]. Because of this, different kinds of parameters are able to characterize the changes taking place in the tumor at each stage of therapy. Meanwhile, a multi-parameter approach combining statistical analysis with spectral analysis was proposed by Piotrzkowska-Wróblewska *et al*.[27]. The study participants included a group of patients with lesions of varying size, referred for neoadjuvant treatment. US data was recorded one week after each NAC course and immediately before surgery. Changes in the parameter values, occurring in tumors, were presented by the authors using parametric maps. An example of a series of quantitative images for a responder and non-responder is shown in Fig. 3 and Fig. 4.

Using the IBC and ENS parameter values, on a group of 24 tumors, Piotrzkowska-Wróblewska *et al*. showed that the simultaneous use of spectral analysis and the statistical evaluation of the signal envelope allowed for the differentiation between responders and non-responders after the second and third course of chemotherapy, with AUC = 0.82 and AUC = 0.91, respectively[16]. In a single-parameter assessment, for IBS, the respective AUC values were AUC = 0.7 and AUC = 0.81, and, for ENS, they were AUC = 0.79 and AUC = 0.80.

The analysis of the test results presented in the above-mentioned studies indicate the potential of QUS as a tool for predicting the response of patients with breast cancer to the applied treatment in the form of NAC.

The advantages of quantitative methods were also demonstrated by Dobruch-Sobczak *et al*., who showed (based only on ultrasonic images) that changes in tumor echogenicity are closely related to the level of cancer lesion response to treatment. Moreover, based on changes in tissue echogenicity in B-mode after the third course of chemotherapy, these authors were able to predict a decrease in tumor cellularity with a sensitivity of 84% and specificity of 93%[28].

However, it should be noted that the observation and assessment of the level of changes in tissue echogenicity based on image analysis may be a great challenge, as its evaluation may be influenced by both the operator's experience and image settings. However, the approach proposed by Dobruch-Sobczak *et al*. can be fully objective through using the IBC parameter which quantitatively provides information about the scattering properties of microstructures present in the medium and thus characterizes tissue echogenicity in a quantitative manner[29]. In another study, which was a continuation of the above-discussed topic, Dobruch-Sobczak *et al*. confirmed this hypothesis[30].

The application of QUS methods is associated with the parameterization of tissues and thus enables the comparison of test results performed by different operators and using varying equipment.

This information was confirmed by DiCenzo *et al*., who were the first to publish the results of multi-center studies

(four centers) using QUS to evaluate the effectiveness of NAC[31]. The results showed high reproducibility of the results, regardless of whether the analyzed data came from only one center or four. The method proposed by the authors for the assessment of the prediction of the effectiveness of NAC – based on an analysis of the texture of quantitative images generated on the basis of spectral parameters (e.g., a total of 24 texture parameters obtained as a result of analyzing parametric images generated on the basis of six spectral parameters) – was characterized by a sensitivity of 91%, specificity of 83%, and accuracy of 87% when identifying patients as either responders or non-responders in the fourth week after the start of therapy.

The same team also proved that the use of different US systems for data acquisition was not an obstacle to the use of QUS in the context of detecting response to treatment. The research was carried out both with the participation of patients and in vitro, with the use of phantoms. The data was recorded using a variety of US scanners, including UltrasonixRP (Ultrasonix Medical Corp., Richmond, BC, Canada) and GELOGIQ E9 ([GE] Healthcare, Milwaukee, WI, USA). The observed differences in the data between the systems were minor, and the forecast results from the two systems did not show any significant statistical differences[32].

Conclusions

The presented results regarding the application of QUS show the potential of this method in predicting tumor response to NAC.

Obviously, studies involving large groups of patients are necessary to fully confirm the usefulness of QUS in predicting responses to NAC. However, it should be remembered that such studies are difficult and time-consuming. Collecting data from only one patient requires the recording of signals, in accordance with the schedule of taking NAC, over a period of several months. Therefore, long-term cooperation of specialists in the field of ultrasonography and doctors is necessary, as well as participation in the examinations of oncological patients. The analysis of reports published by individual research groups shows that these teams gradually increase the number of patients participating in their studies.

There are, of course, limitations that may make it difficult to use quantitative ultrasonography to predict responses to NAC. Large tumors, with size exceeding the size of the transducer, may prove problematic. It is then difficult to simultaneously "see" and, as a consequence, analyze the entire tumor. On the other hand, small tumors should also be mentioned. The results of the study show that the quantitative analysis is possible even in the case of very small tumors, the diameter of which does not exceed 5 mm. Additionally, in order to avoid problems with the correct localization of the tumor, which may become invisible on the ultrasound image as a result of NAC, special markers are used which are placed in the tumor before treatment is started.

The implementation of QUS methods in clinical practice would make it possible to monitor tumors after each treatment cycle, and, in the case of no response, enable the modification of the therapy to be more effective in the early stages of treatment. Promising research results allow us to believe that in the near future these methods will be implemented by manufacturers as software extending the diagnostic capabilities of ultrasound, while organizations such as the World Federation of Ultrasound in Medicine and Biology will release guidelines on the clinical use of QUS imaging methods for monitoring the response of breast tumors to NAC.

Consequently, such a procedure would make it possible to offer patients a more personalized treatment and thus increase therapeutic efficacy.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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Author contributions

Original concept of study: HP-W. Writing of manuscript: HP-W, KD-S. Final acceptation of manuscript: HP-W. Critical review of manuscript: KD-S, JL.

References

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M *et al.*: Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer 2018; 103: 356–387.
2. Giordano SH: Update on locally advanced breast cancer. Oncologist 2003; 8: 521–530.
3. Wojciechowska U, Didkowska J, Michałek I, Olasek P, Ciuba A: Cancer in Poland in 2018. Polish National Cancer Registry, Warsaw 2020.
4. Vaidya JS, Massarut S, Vaidya HJ, Alexander EC, Richards T, Caris JA *et al.*: Rethinking neoadjuvant chemotherapy for breast cancer. BMJ 2018; 360: j5913.
5. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R *et al.*: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228–247.
6. Gruber IV, Rueckert M, Kagan KO, Staebler A, Siegmann KC, Hartkopf A *et al.*: Measurement of tumour size with mammography,

sonography and magnetic resonance imaging as compared to histological tumour size in primary breast cancer. BMC Cancer 2013; 13: 328.

7. Vriens BE, de Vries B, Lobbes MB, van Gastel SM, van den Berkmortel FW, Smilde TJ *et al.*: Ultrasound is at least as good as magnetic resonance imaging in predicting tumour size post-neoadjuvant chemotherapy in breast cancer. Eur J Cancer 2016; 52: 67–76.
8. Zhang K, Li J, Zhu Q, Chang C: Prediction of pathologic complete response by ultrasonography and magnetic resonance imaging after neoadjuvant chemotherapy in patients with breast cancer. Cancer Manag Res 2020; 12: 2603–2612.
9. Loo CE, Straver ME, Rodenhuis S, Muller SH, Wesseling J, Vrancken Peeters MJ *et al.*: Magnetic resonance imaging response monitoring of breast cancer during neoadjuvant chemotherapy: relevance of breast cancer subtype. J Clin Oncol 2011; 29: 660–666.
10. De Los Santos JF, Cantor A, Amos KD, Forero A, Golshan M, Horton JK *et al.*: Magnetic resonance imaging as a predictor of pathologic response in patients treated with neoadjuvant systemic treatment for operable breast cancer. Cancer 2013; 119: 1776–1783.
11. Aldrich JE: Basic physics of ultrasound imaging. Crit Care Med 2007; 35 (5 Suppl.): 131–137.
12. Staren ED: Physics and principles of breast ultrasound. Am Surg 1996; 62: 103–107.
13. Hooley RJ, Scoutt LM, Philpotts LE: Breast ultrasonography: state of the art. Radiology 2013; 268: 642–659.
14. Sheereen S, Lobo FD, Kumar B, Kumar SM, Reddy GS, Patel W *et al.*: Histopathological changes in breast cancers following neoadjuvant chemotherapy: implications for assessment of therapy-induced cytological and stromal changes for better clinical outcome and effective patient care. Asian J Oncol 2018; 4: 61–68.
15. Cloutier G, Destrempes F, Yu F: Quantitative ultrasound imaging of soft biological tissues: a primer for radiologists and medical physicists. Insights Imaging 2021; 12: 127.
16. Oelze M, Mamou J: Review of quantitative ultrasound: envelope statistics and backscatter coefficient imaging and contributions to diagnostic ultrasound. IEEE Trans Ultrason Ferroelectr Freq Control 2016; 63: 336–351.
17. Mamou J, Oelze M: Quantitative Ultrasound in Soft Tissues. Springer, 2013.
18. Oelze M: Quantitative ultrasound successes: past, present and future. Proc SPIE 11319, Med Imaging 2020: Ultrasonic Imaging and Tomography, 113190X.
19. Sadeghi-Naini A, Papanicolau N, Falou O, Zubovits J, Dent R, Verma S *et al.*: Quantitative ultrasound evaluation of tumor cell death response in locally advanced breast cancer patients receiving chemotherapy. Clin Cancer Res 2013; 19: 2163–2174.
20. Sannachi L, Tadayyon H, Sadeghi-Naini A, Tran W, Gandhi S, Wright F *et al.*: Non-invasive evaluation of breast cancer response to chemotherapy using quantitative ultrasonic backscatter parameters. Med Image Anal 2015; 20: 224–236.
21. Taleghamar H, Moghadas-Dastjerdi H, Czarnota GJ, Sadeghi-Naini A: Characterizing intra-tumor regions on quantitative ultrasound parametric images to predict breast cancer response to chemotherapy at pre-treatment. Sci Rep 2021; 11: 14865.
22. Tadayyon H, Sadeghi-Naini A, Czarnota GJ: Noninvasive characterization of locally advanced breast cancer using textural analysis of quantitative ultrasound parametric images. Transl Oncol 2014; 7: 759–767.
23. Hruska DP, Oelze ML: Improved parameter estimates based on the homodyned K distribution. IEEE Trans Ultrason Ferroelectr Freq Control 2009; 56: 2471–2481.
24. Dutt V, Greenleaf JF: Ultrasound echo envelope analysis using a homodyned K distribution signal model. Ultrason Imaging 1994; 16: 265–287.
25. Klimonda Z, Karwat P, Piotrzkowska-Wróblewska H, Dobruch-Sobczak K, Litniewski J: Ultrasound scattering statistics predicts the result of neoadjuvant chemotherapy of breast tumors at an early stage of treatment. IUS 2019, IEEE International Ultrasonics Symposium 2019: 1–3.
26. Sethi D, Sen R, Parshad S, Khetarpal S, Garg M, Sen J: Histopathologic changes following neoadjuvant chemotherapy in various malignancies. Int J Appl Basic Med Res 2012; 2: 111–116.
27. Piotrzkowska-Wróblewska H, Dobruch-Sobczak K, Karwat P, Roszkowska-Purska K, Litniewski J: Monitoring breast cancer response to neoadjuvant chemotherapy with ultrasound signal statistics and integrated backscatter. PLoS One 2019; 14: e0213749.
28. Dobruch-Sobczak K, Piotrzkowska-Wróblewska H, Klimonda Z, Roszkowska-Purska K, Litniewski J: Ultrasound echogenicity reveals the response of breast cancer to chemotherapy. Clin Imaging 2019; 55: 41–46.
29. Dobruch-Sobczak KS, Piotrzkowska-Wróblewska H, Karwat P, Klimonda Z, Markiewicz-Grodzicka E, Litniewski J: Quantitative assessment of the echogenicity of a breast tumor predicts the response to neoadjuvant chemotherapy. Cancers (Basel) 2021; 13: 3546.
30. Dobruch-Sobczak K, Piotrzkowska-Wróblewska H, Klimoda Z, Secomski W, Karwat P, Markiewicz-Grodzicka E *et al.*: Monitoring the response to neoadjuvant chemotherapy in patients with breast cancer using ultrasound scattering coefficient: a preliminary report. J Ultrason 2019; 19: 89–97.
31. DiCenzo D, Quiaoit K, Fatima K, Bhardwaj D, Sannachi L, Gangeh M *et al.*: Quantitative ultrasound radiomics in predicting response to neoadjuvant chemotherapy in patients with locally advanced breast cancer: results from multi-institutional study. Cancer Med 2020; 9: 5798–5806.
32. Sannachi L, Gangeh M, Naini AS, Bhargava P, Jain A, Tran WT *et al.*: Quantitative ultrasound monitoring of breast tumour response to neoadjuvant chemotherapy: comparison of results among clinical scanners. Ultrasound Med Biol 2020; 46: 1142–1157.