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Towards refining breast cancer diagnosis on ultrasound

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Breast cancer (BC) is the most common malignant neoplasm in the world regardless of gender (with 2,261,419 cases registered in 2020, representing 11.7% of all cases) and it is characterized by a high mortality rate (6.9% – 684,996 cases)[1]. Therefore, any action aimed at improving the effectiveness of screening and diagnosis of this cancer, especially with the application of minimally invasive, safe, and accessible methods such as ultrasonography (US), contributes to the reduction of both statistics. The use of US for screening and diagnosis can take place in a variety of situations, from strategic application in specialized breast centers to remote medicine settings[2,3].

The literature review by Dobruch-Sobczak *et al.*[4], based on an unidentified search engine, seeks to identify the most important topics relating to a molecular understanding of breast cancer and to distinguish the ultrasound features of the individual intrinsic subtypes.

While reading the article, I asked myself if there were any reliable diagnostic features of breast cancer to be found by ultrasound. Going further, I pondered whether it was possible to recognize the intrinsic subtypes of breast cancer by ultrasound, and thus predict tumor biology based on indirect information from the imaging test. The first problem is particularly important in young women, in whom the role of ultrasound – as the authors noted – cannot be overestimated due to the structure of the breasts. For example, a 20-year-old female patient presents with a lump in the breast, for an ultrasound test, and does not expect to receive a diagnosis by biopsy; therefore a senologist-ultrasonographer is faced with the dilemma whether to classify the condition as BI-RADS 3 or BI-RADS 4, considering that the risk of developing breast cancer within 10 years from the age of 20 is 1:1760 (0.06%)[5]. The second issue concerns the nature of counselling offered to the patient, because if the US permits identification of the gene expression patterns of different molecular subtypes of BC, the patient must be informed of the specific diagnosis and associated course of treatment before undergoing biopsy and receiving the associated histopathological result. The third issue is to determine the type of biopsy to be administered, which is related to tumor size and the degree of cancer suspicion. The fourth is related to the expected costs of the suite of examinations that the pathologist should perform. Moreover, by identifying and accurately describing tumor biology in ultrasound, we can more precisely track tumor regression during neoadjuvant chemotherapy, which brings us closer to a better correlation of histopathology and molecular biology of the cancer with its imaging characteristics, and thus, enables better decisions for patients. I believe that the above-mentioned elements could complement the introduction to the quoted article. In my opinion, the oncological aspects raised in the introduction are less important in this context, as the authors rarely look for a relationship in the main body of their paper (e97 and next page).

Working as a gynecologist-senologist, with most of my patients being pre-screening age (under 35), I wonder how to distinguish the features of a supposedly benign lesion from triple-negative breast cancer. Tian *et al.*, in a meta-analysis of 10 studies that included a total of 620 patients, found that assessing triple negative breast cancer (TNBC) by ultrasound does not reveal any particularly distinctive features of cancer, such as irregular shape, non-circumscribed margins, echogenic halo, nonparallel orientation, posterior acoustic attenuation, microcalcification, etc.[6] In contrast, fibroadenoma (FA), the main representative of the BI-RADS-US 3 category, has several typical ultrasound features distinguishing two histopathological subtypes – florid and regressive[7]. As Zhang *et al.* attempted to distinguish two subgroups of TNBC ultrasound features, creating two different patterns (resembling changes in BI-RADS-US 3 and BI-RADS-US 4)[8], the intrinsic subtype itself was also found to be heterogeneous (and in the ultrasound image). Histopathology is required to explain the fact that TNBC does not resemble "normal" cancer. An in-depth histopathological analysis shows what differences should be expected with both fibroadenoma and cancer subtypes[9]. I tried to outline these features in Tab. 1.

A team decision, as suggested by Zhang *et al.*,[8] cannot be made in every case of a diagnosed lesion – for example in Poland it is still difficult to implement team-based approaches (because there are few breast units, and "eminence-based medicine" persists in many establishments). From a biological perspective, however, especially in tumor subtypes associated with poor outcomes, such as TNBC or HER-2 (human epidermal growth factor receptor 2) overexpression subtype or triple-positive (luminal B HER-2 enriched), scanning in the B-mode alone is not sufficient. There is a need for a multiparameter examination including, in addition to the B-mode, the

Tab. 1. Summary of histopathological and ultrasound features of different intrinsic subtypes of breast cancer

Intrinsic subtype	Main histopathological features[9]	Main ultrasound features[4]
Luminal A	MA: poorly demarcated tumor of soft texture, 25% multifocal (ILC) MI: diffuse-infiltrative growth without focal findings	Hyperechogenic halo, spiculae
Luminal B (incl. "HER-2 enriched")	MA: knotty, of firm consistency and has radial spurs MI: polygonal, cohesive tumor cells, infiltrating-destructive growth	Increased vascularity, lack of halo
HER-2 positive*	MA: locally restricted, multifocal MI: presence of DCIS	Calcifications, multifocality
TNBC	MA: Well-defined tumor with soft texture, focal necrosis, or hemorrhage within the tumor MI: syncytial architecture	Lobular margins, acoustic enhancements

DCIS – ductal carcinoma in situ; HER2 – human epidermal growth factor receptor 2; ILC – invasive lobular carcinoma; MA – macroscopic; MI – microscopic; TNBC – triple-negative breast cancer
* The frequency of HER-2 positive cancers depends on cancer stage; HER2 (human epidermal growth factor receptor 2) positive cancers mark a separate molecular pathway of carcinogenesis

color Doppler and elastography. Addressing the extensive literature on this subject would lead to an excessively long letter.

Although the illustrative analysis performed by Dobruch-Sobczak *et al.*[4] does not permit such conclusions to be drawn, as I attempt to summarize in Table 1, in fact it is and should be an appeal to use additional ultrasound applications, such as color Doppler or elastography, in the assessment of changes in the breasts.

Summing up, I believe that the article by Dobruch-Sobczak *et al.*[4] on the subject of "ultrasound profiling" of breast cancer will lead us to a place where we will be able to say "this is TNBC and this is luminal A". We are nearer to this goal rather than farther away, considering the success of Polish scientists in terms of the possibility of using Jagiellonian-PET in oncological diagnostics[10]. A manifestation of the natural development of ultrasonography is radiomics and the use of artificial intelligence methods to predict changes[11]. However, it should be remembered that there is a human behind all algorithms and systems, and the patient is not a computer. The final decision always comes down to data analysis, experience, and even intuition.

Conflict of interest

The author does 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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