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Diversity of breast cancers begins at imaging…

Breast cancer always has been a pioneering field of new concepts and innovations in oncology. The first observations on the stimulatory effects of sex hormones and the anticancer effect of ovarian ablation [1], the discovery of the hormone receptors [2] and the synthesis of the estradiol antagonist tamoxifen [2], the detection of the c-erbB2 molecule as a poorest prognostic factor [3] and the success story of its annihilating monoclonal antibody trastuzumab [4] or the introduction of a variety of safe breast surgeries all stoned the way to the need of characterisation and tailored management of breast cancers. In fact mammography breast screening by advancing diagnosis in most cases, has added a lot to learning the landscape of breast cancers at a true early stage of more significant diversity [5]. First, the status "screening-detected" *per se* has proved to be an independent favorable prognostic factor possibly implemented in treatment decision [5–7]. Second, a consistent classification system based on mammographic appearance emerged that may serve as a frame for the recent proceeds that are considered as elements of precision oncology. Indeed there is a demand of paradigm change in management which is nowadays called precision oncology meaning "… detailed knowledge of the inherent biological propensities of each tumor, rather than generalizing treatment approaches based on phenotypic, or even genotypic, categories" as Harris refers to it [8]. For this approach that simultaneously serves more efficient treatment outcome and less burden on the patient, various sometimes rivaling molecular methods are available that consider genomic, transcriptomic, proteomic, metabolic etc. alterations of the tumor. Many of these tests are extensively used with great utility most importantly influencing oncology care. In the field of breast cancer, mammography, ultrasound and MRI features are considered as imaging biomarkers playing an integral role in complex management [9]. These, in the language of precision medicine called "radiomics" in contrast to molecular investigations, carry the advantages of showing the entire cancer and reflecting its distribution, vascularisation and metabolism. Although the use of imaging biomarkers for cancers is encouraged strict assumptions are suggested for their validation [10]. One among these is their evaluation based on long-term disease outcome.

Recently in the European Journal of Radiology, a general introduction to a series of articles has appeared presenting a novel breast cancer imaging biomarker system based on decades of intensive research [11]. In this thorough work, mammography images of many thousands of women participating in either randomized trials or mammography service screening have been correlated with large format conventional and thick section histopathology and over 4 decades of patient follow-up data.

The study population represented patients participating in systematic screening with breast cancers diagnosed at their earliest detectable phase. The majority belonging to the "acinar adenocarcinoma of the breast (AAB)" group showed excellent prognosis while 2 subgroups identifiable by their unique mammographic appearance (one with the presence of intraductal microcalcification called "ductal adenocarcinoma of the breast, DAB", and the other with parenchyma distortion due to interstitial fibrosis called "breast carcinoma of mesenchymal origin, BCMO") despite being detected at screening had a dismal outcome similar to that in symptomatic advanced cases (Fig. 1). What is the explanation for the striking difference in the natural behaviour of these entities? Tabár et al. found the answer in the difference of tissue compartments where these cancers could be localized. The largest otherwise heterogeneous group of AABs showed the involvement of the TDLUs and carried a favourable outcome. In contrast, those which were situated outside of the TDLU were of poor prognosis. The DAB group involved the major lactiferous ducts with the unique histopathologic feature of neoductgenesis. In the BCMO group, cancer cells diffusely infiltrated around the ducts inducing progressive fibrosis while mimicking MET and EMT.

Interestingly, in both the DAB and BCMO groups the extent of the disease and hence cancer load was huge compared to that in the AAB group, and outcome was even worse if lymph node metastases were present [11,12]. Why were these screening-detected cancers so advanced? Do they have an accelerated natural course? Do they proliferate at a higher turnover pace? A higher proliferation rate is not likely if we consider the grade or other proliferation markers. Do they spread more smoothly in a different anatomical structure or under a different control? If the significance of this phenomenon emerges a more frequent screening possibly could detect them earlier. Or are the presently used imaging methods blind to detect these very types at an early phase (hence an alternative screening method should be introduced?)? Do these subtypes develop out of a sudden in a large volume from their start off? Who are the risk patients? Could individualized breast screening work? What could be the role of MRI in this respect?

The stimulating work of Tabár et al. and the suggested breast cancer terminology opens new perspectives both in research and routine management.

Tabár's well-established revolutionary findings rouse one's imagination how much could be gained in research by implementing those already existing breast cancer investigational data which could be reanalyzed by retrospectively adding the tumours' imaging biomarkers. As Tabár et al. stress since the management of AABs is more or less solved, special efforts should be put into the investigation of the special types of DAB and BCMO with emphasis on the key biological processes (neoductgenesis in DAB and mesenchymal stem cells and MET/EMT) presented.

The utilization of the new approach is equally important also in

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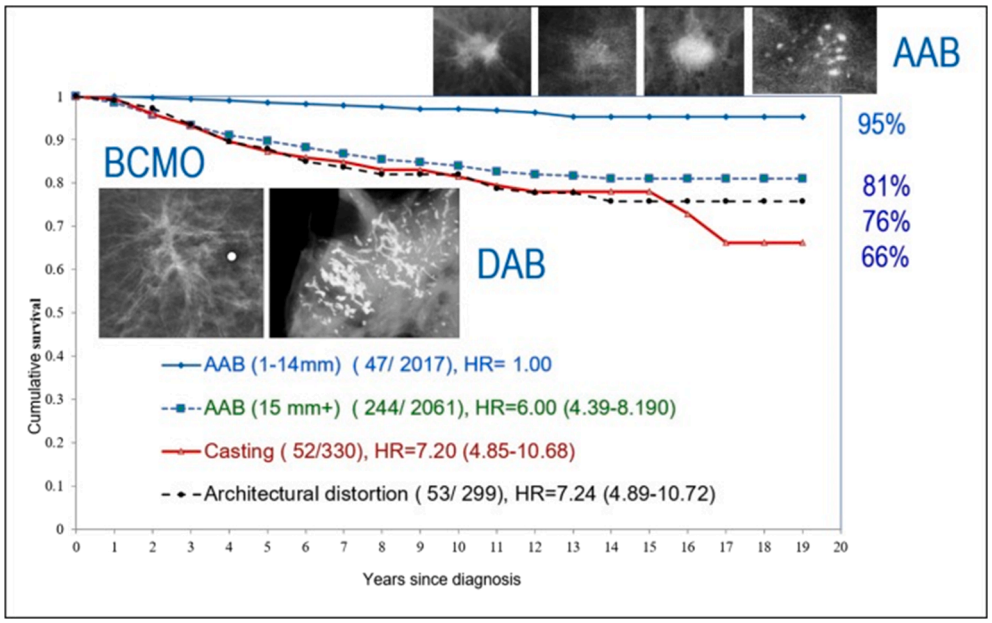

Fig. 1. In multidisciplinary tumour boards the starting point should be the consideration of the imaging biomarkers including the mammographic appearance, tumor extent and tumor distribution to instruct strategy. *Note:* This figure was published in the European Journal of Radiology, volume 149 (April 2022), László Tabár et al., "A new approach to breast cancer terminology based on the anatomic site of tumour origin: The importance of radiologic imaging biomarkers", article 110189, Copyright Elsevier B.V. (2022).

patient care. First of all current histopathology terminology and practice seem to be misleading in many ways. There is a need of radically reforming the present TNM/AJCC system by including the screening-detected status and the new imaging biomarkers. What other prognosticators if not mammography appearence could be used for considering biological behaviour and even treatment effectiveness? The main goal is to introduce and accept the new terminology and classification and, the use of large format section in histopathology practice. Surgical care should be even more driven by the knowledge of the new imaging biomarker status of the case. Finally, oncology practice should utilize the new imaging biomarkers within the approach of precision oncology during treatment decision and when implementing novel medical therapies. Accordingly, in multidisciplinary tumour boards the starting point should be the consideration of the imaging biomarkers including the mammographic appearance, tumor extent and tumor distribution to instruct strategy.

The very consistent imaging biomarker system presented in the article series by Tabár et al. based on mammographic and MRI images, various histopathologic findings, long-term outcome of patients and basic research [11] meets all the requirements summarized in a recent international consensus document on imaging biomarkers including utility for testing research hypotheses, clinical decision making tool, measure a relevant aspect of biology or predict clinical outcome, cost-effectiveness, geographical availability [10].

Of note, the fundaments of this new breast cancer classification and imaging biomarker system are already known worldwide thanks to the tireless educational activity and international scientific cooperation of the first author [13–17]; its wide-spread implementation holds great potential in supporting precision care of breast cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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