Pathology & Oncology Research

Guidelines from the Central-Eastern European Professional Consensus Statement on Breast Cancer

Issue Editors

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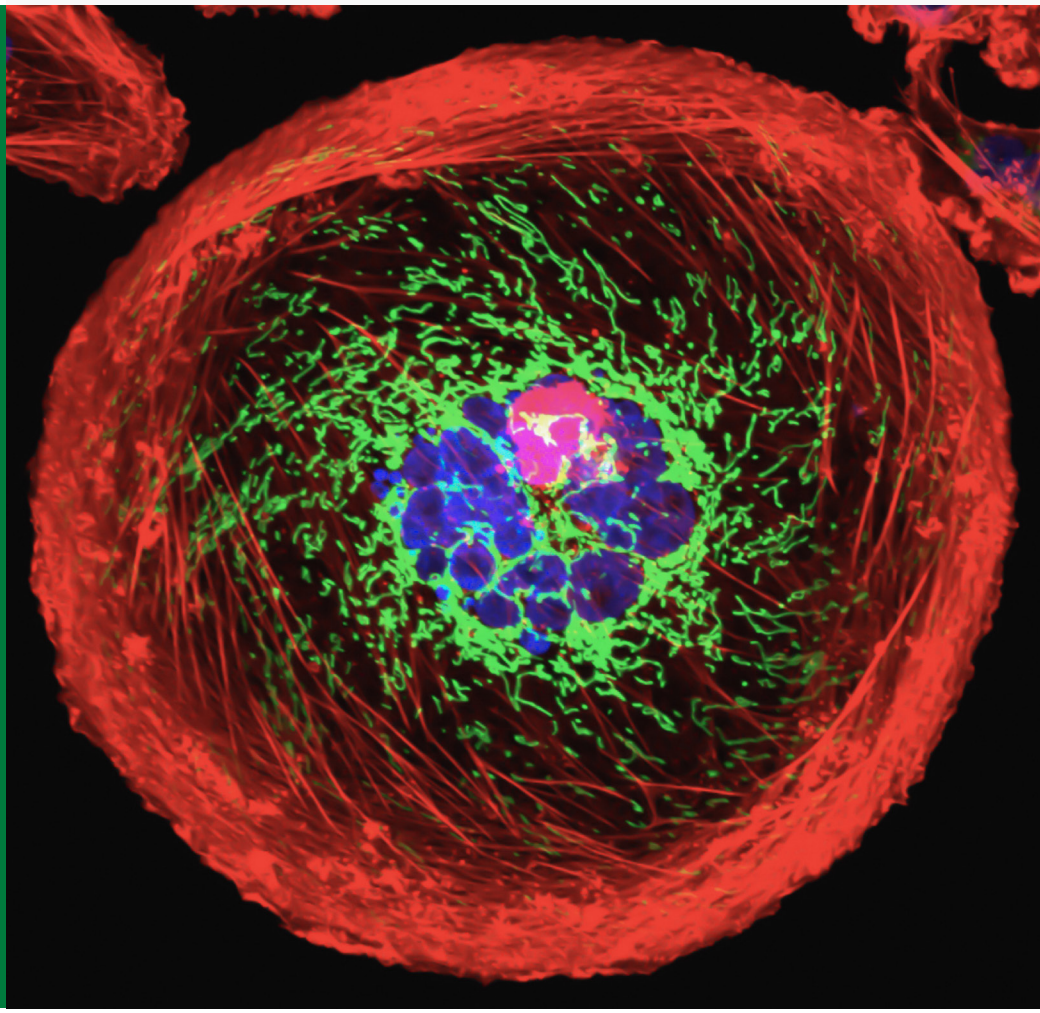

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Guidelines from the Central-Eastern European Professional Consensus Statement on Breast Cancer

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The contributions contained in this collection comprise the recommendations accepted by the Consensus Conference organized on 6-7 November 2021 in Visegrád, Hungary, and form the 1st Central-Eastern European Professional Consensus Statement on Breast Cancer. The content is based on English-language translations from the original Hungarian of recommendations accepted by the 4th Hungarian Consensus Conference on Breast Cancer, adjusted to include the frames of the Central-Eastern European Academy of Oncology and updated by changes in practices and recommendations introduced during the nearly one-year-period between the two consensus conferences. Additionally, these guidelines fall within the recommendations of ESMO, NCCN and ABC5, as well as that of the St. Gallen Consensus Conference statements.

The guidelines cover problematics of breast cancer diagnosis, treatment, and management, with specific chapters on:

- screening, imaging, and diagnostic modalities for breast tumours
- pathology and reporting of breast cancer*
- contemporary breast cancer surgery*
- radiotherapy of breast cancer
- systemic treatment of breast cancer*
- follow up, rehabilitation, and psycho-oncology

Chapters labelled with an asterisk (*) have been substantially updated / modified following the publication of the 4th Hungarian Consensus Conference recommendations.

The original guidelines may be found in full-text with the Hungarian publication Magyar Onkológia 2020 (64) 4: 277-398, at huon.hu.

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EDITORIAL
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Editorial: Guidelines From the Central-Eastern European Professional Consensus Statement on Breast Cancer

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Keywords: breast cancer, imaging, pathology, surgery, radiotherapy, systemic treatment, follow-up and rehabilitation, psycho-oncology

Editorial on

Guidelines from the Central-Eastern European Professional Consensus Statement on Breast Cancer

Multidisciplinary management of breast cancer patients has become standard of care. It has been shown that patients managed by multidisciplinary teams have better disease outcome and better quality of life. In a large retrospective cohort study analyzing outcome data of 13,722 breast cancer patients diagnosed between 1990 and 2000 at an NHS Hospital in Scotland, it was shown that after the introduction of multidisciplinary care, breast cancer mortality was 18% lower compared to hospitals performing traditional care (1).

Guidelines of various disciplines are being updated regularly as developments in the respective fields evolve rapidly. Furthermore, guidelines developed in different continents and countries around the globe adjust their standards not only to recent and widely acknowledged evidence-based developments but take also into account regional/national opportunities, respective quality assurance measures and health care system structure. Wherever professional guidelines are set, their ultimate and uniform aim is to provide and certify the highest possible standards and quality of patient care.

In Hungary, specialists involved in breast cancer patients' management were the first to recognize the need of a national multidisciplinary document setting basic standards for the respective specialities. In order to develop a consensus document, a multidisciplinary conference was organized in Eger in 1999. The document was approved by the respective professional colleges and from then on the "Consensus Conference Document" became a reference for all medical specialists involved in breast cancer patients' management. Ten years later, and thereafter on three occasions in the following years, the Consensus Document was updated regularly within the frame of the Kecskemét Consensus Conferences. The last edition of these Consensus Documents was published in 2020 in Hungarian Oncology (2–7). As concerns their development, six panels of experts (one for each document covering the fields of breast screening and imaging; pathology diagnosis; surgery; radiotherapy; systemic treatment; follow-up, rehabilitation and psycho-oncology) were invited to draft a document on the basis of previous editions and novel changes in practices and recommendations around the world, and make it available for public consultation 1–2 months before the Consensus Conference. Professionals, including members of the other professional panels were invited to comment the recommendations in the documents in writing or at the Consensus Conference, and the

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texts were amended according to the relevant comments received prior to acceptance by the panel and publication.

Since Central European countries share many similarities including the incidence of breast cancer, health care structure and both financial and instrumental opportunities of cancer treatment in general and in breast cancer treatment in particular, it was a logical step to share and discuss the most recent Consensus Document in a wider circle of Central and Eastern European countries' specialists. The initiative came to birth with the help of a ministerial support and the enthusiastic work of a leading breast oncoplastic surgeon, Dr. Zoltán Mátrai, founding member of the Central-Eastern European Breast Cancer Surgical Consortium (CEEBCSC) and first president of the Central and Eastern European Academy of Oncology (CEEAO).

The development of the final version of the texts published in this Issue of Pathology & Oncology Research followed a methodology similar to the formulation of the Hungarian Consensus Documents; i.e., the Hungarian documents (2–7) were translated, updated where deemed necessary, circulated to institutions involved in the CEEAO and their networks, modified according to comments, made available for public discussion prior to a hybrid Consensus Conference held in Visegrád, Hungary on 5–7 November 2021. This resulted in the final adjustment of the recommendations formulated through partners in the CEEAO following the international discussions, and the production of a set of up-to-date guideline-type documents that reflect the gold standard of breast cancer patients' management in our region. Meanwhile it has to be emphasized that all documents included in the Issue incorporated the basic standards of the most recent European and American guidelines.

The set of documents published in this issue of Pathology & Oncology Research (8–13) comprises the guidelines for the major specialties involved in breast cancer management: radiology and nuclear medicine for imaging, pathology, surgery, medical- and radiation oncology and rehabilitation, including psycho-oncology. Compared to the 2020 texts of the Hungarian recommendations, the pathology (9), surgery (10) and medical oncology (12) texts have been substantially updated, the radiation oncology text had minor modification, whereas the other two texts had no mentionable changes.

In the first document (8), standards of multimodality imaging from mammography to isotope localization techniques, imaging follow-up of cancer patients and technical requirements of the instruments are described in line with the most recent specific professional guidelines.

The second document on pathology workup and reporting (9) includes guidance from processing of the material to its reporting and content of the report, an updates also cover the use of digital- and molecular pathology methods acceptable as standards.

The third text (10) includes the modern approach of oncoplastic surgery and suggests to treat breast cancer patients in centers where this modality is available.

The fourth document (11) summarizes the evidence-based modern methods and technical requirements of radiation oncology used in the adjuvant treatment of breast cancer patients.

The fifth document on medical oncology (12) describes in detail state-of-the art medical treatment of breast cancer patients, including the most recent opportunities provided by immune therapies and therapies based on the results of multigene molecular testing of tumors.

The sixth document gives guidance for follow up, rehabilitation and psycho-oncology (13) and is an important chapter in the Issue which was accepted by the International Consensus Committee. We believe that publishing these guidelines will help medical teams to achieve high standards of breast cancer patients' management and breast cancer patients to have better outcome of their disease.

AUTHOR CONTRIBUTIONS

The Editorial was written by JK and GC. JK drafted and GC finalized. JK and GC have approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the formulation of this text was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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GUIDELINES
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Use of Diagnostic Imaging Modalities in Modern Screening, Diagnostics and Management of Breast Tumours 1st Central-Eastern European Professional Consensus Statement on Breast Cancer

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Breast radiologists and nuclear medicine specialists updated their previous recommendation/guidance at the 4th Hungarian Breast Cancer Consensus Conference in Kecskemét. A recommendation is hereby made that breast tumours should be screened, diagnosed and treated according to these guidelines. These professional guidelines include the latest technical developments and research findings, including the role of imaging methods in therapy and follow-up. It includes details on domestic development proposals and also addresses related areas (forensic medicine, media, regulations, reimbursement). The entire material has been agreed with the related medical disciplines.

Keywords: mammography, breast ultrasound, breast MRI, breast screening, conventional nuclear medicine, SPECT/CT, PET/CT, biopsy

INTRODUCTION

Radiologists and nuclear medicine specialists specializing in the diagnostics of breast diseases have compiled their opinions on diagnostic imaging and screening for breast cancer. Based on international evidence, it is hereby recommended that the radiological and nuclear medicine aspects of breast cancer diagnosis and management are conducted in accordance with these guidelines. This material was discussed and accepted by the 4th Breast Cancer Consensus Conference on 28–29 August 2020. It was then submitted to the Radiology Section of the National Advisory Board, which has approved it. Regular updates of the material are still recommended.

PURPOSES OF DIAGNOSTIC IMAGING METHODS IN BREAST TUMOURS

- Breast tumour screening, detection, confirmation (1).
- Guiding targeted biopsy: preoperative/pre-therapeutic sampling to establish cytological/histological diagnosis, whenever requested.
- Assessment of locoregional extent.
- As part of therapeutic planning, staging.
- As part of therapy: preoperative localization of the tumor bed or tumor site with markers effective neoadjuvant therapy, confirmation of a tumour in the specimen, helping with pathological processing, percutaneous minimally invasive therapy in selected cases.
- Evaluation of therapy effectiveness.
- Follow-up studies.
- Early detection of recurrence.
- Participation in new staging.

The basic principle: No breast therapy may be performed without imaging studies.

BREAST INVESTIGATION MODALITIES

Mammography

Mammography is mandatory for symptoms or complaints developing in patients aged over 30–35 years. In justified cases, it can be carried out in patients aged under 30. Mammography is the only scientifically proven method for screening asymptomatic women at average risk with the purpose of reducing breast cancer mortality (2). Direct digital mammography has been shown to perform better than conventional analogue techniques (3). As the screening age for mammography varies from country to country, the age cut-off for mammography and US scans should be adjusted accordingly.

Tomosynthesis

Digital breast tomosynthesis (DBT) is a procedure based on full-field digital mammography (FFDM) in which an X-ray tube moving in an arc capturing 10–15 overlapping digital images of the breast in a short time at low radiation doses. Data are computer- processed, resulting in thin slice images and can be reconstructed to summation images called "synthetic 2D images," which look similar to conventional images. In order to reduce radiation dose, it is recommended that conventional 2D images be partially or completely replaced with synthetic 2D images, provided that the device has an official certificate (e.g., FDA approval). 3D tomosynthesis is more sensitive for the assessment of breast structure, and hidden lesions are easier to be detected (higher sensitivity). Tomosynthesis is highly efficient (higher specificity) in assessing overlapping tissues (summation) that pose diagnostic difficulties during conventional 2D imaging. By analysing images cut into thin slices, breast structure can be assessed without the disturbing effects of overlapping, so that pathological structural distortions and lesion borders can be evaluated more accurately, and false-positive results resulting from summation can be eliminated. As a result, 29%–41% more tumours can be detected and, if applied during screening, recall rates are significantly reduced, and unnecessary biopsies can be avoided. Use of tomosynthesis in breast screening is particularly advantageous for breast structures (dense fibrotic, fibroadenotic tissue) for which conventional mammography has a lower sensitivity (4, 5).

Contrast-Enhanced Spectral Mammography

One of the latest developments in digital mammography is the use of intravenous iodinated contrast media for dual-energy mammography. The subtraction technique allows for analysis of contrast accumulation in breast lesions, similarly to breast MRI. According to some studies, CESM may be suitable for the assessment of abnormalities detected by mammography, especially for dense breast structures, to evaluate the extent of the disease. According to some reports, its sensitivity is close to that of a breast MRI, but this has not yet been clearly established for DCIS. Radiation exposure is 81% higher than for a conventional 2D digital mammography, and 48% higher than for DBT (6–8). Currently, this modality is being researched and may only be used with serious reservations, and it must never be a substitute for indications that have long been supported by evidence (e.g., mammography, breast MRI) (9, 10).

Ultrasound Scanning of the Breast

Breast ultrasound can be used on its own in patients aged under 30. Over the age of 30–35 years, it can be a complementary procedure to mammography, when needed (11). It is not suitable for breast cancer screening, at any age. As for ultrasound scans of other regions, breast ultrasound scanning should be documented with images in accordance with professional rules, even in negative cases. Colour Doppler is optional, but can be used in addition. Some studies suggest that a significant number of malignancies can be detected by ultrasound scanning as a complement for mammography (12), but this has not yet been routinely introduced due to extra human resource requirements and a high false positive rate.

Automated Breast Ultrasound

Automated breast ultrasound scan hasn't become widespread yet as a complementary investigation modality for dense breast structures (13, 14). Using a probe covering the breast, volumetric data are collected about the entire breast, from which slices can be reconstructed to review the glandular tissue in the main anatomical planes. This modality provides a good anatomical overview, as it is reproducible, and it can be complemented by an automatic image recognition system. Its disadvantage is that the false positivity rate is high for the biopsies it indicates, most of which will be benign (15). It should be emphasized that the resolution and information content of ultrasound images provided by ABUS is the same as for manual ultrasound scanning.

In most states of the United States, for high density breasts, it is mandatory to inform patients about investigations that complement screening mammography (e.g., ultrasound). Mammographic breast density, as an independent risk factor, is still subject to scientific debate; however, the tumour-masking effect of a higher density, which makes tumour detection difficult, is an accepted fact (16).

Hybrid—DBT and ABUS

This is a combination of digital breast tomosynthesis and automated breast ultrasound. This modality is part of a research project, and it is not yet commercially available. This device captures tomosynthetic mammography images in a conventional CC and MLO setup, after which 3D ultrasound images are recorded by an automatic ultrasound device built into the compression plate. Studies have shown that the combination of ultrasound scanning and mammography in screening may significantly improve the rate of detected abnormalities. This method utilizes the advantages of both tomosynthesis and automated ultrasound scanning over the 2D technique (17, 18).

Second-Look (Repeated Targeted) Ultrasound

If an MRI image suggests malignancy, targeted (second look) ultrasound scanning is recommended even if the lesion was hidden on mammography and on the first ultrasound scan. It is important that this is done by a radiologist experienced in breast MRI. By doing this, 60%70% of originally occult lesions can be detected, and ultrasound-guided sampling can be performed (19).

Elastography

Shearwave sonoelastography is a non-invasive imaging procedure based on tissue elasticity, measured in kPA. An abnormal process will modify the elastic properties of the affected tissue (20). According to studies, ultrasound elastography may help differentiate BI-RADS 3 and 4a lesions, and may increase the specificity of ultrasound scanning, thereby reducing the number of unnecessary breast biopsies (21, 22). The role of elastography in the monitoring of neoadjuvant treatments, in the differential diagnosis of suspected axillary lymph nodes, and in the evaluation of microcalcifications affecting the glandular tissue has been investigated. This method has also been integrated into the current BI-RADS lexicon of 2013 (23).

Breast MRI

Indications for Breast MRI

- If a tumour is suspected, but the results of mammography and ultrasound are insufficient or uncertain (24).
- When searching for an occult primary tumour.
- Preoperative assessment of proven cancers, for the evaluation of multiplicity, extent, bilaterality, chest wall involvement—especially if different investigation methods show a difference in size (difference of more than 1 cm between mammography and ultrasound, especially in patients aged under 60).
- Breast MRI has been shown to be of outstanding importance in assessing the extent of an invasive lobular carcinoma (preoperative MRI changes therapy by 28% and significantly reduces the number of reoperations) (25).
- Preoperative MRI is also a useful method for the assessment of DCIS/EIC extent.
- If multifocality is suspected on MRI, efforts should be taken to confirm this histologically; if it cannot be confirmed, the original breast-conserving surgical plan may be overridden by mastectomy only by an oncological team decision or by the patient's wish.
- To increase sensitivity in the screening of dense breasts.
- To differentiate recurrence/scar/granuloma/fat necrosis (not always differentiable without biopsy).
- Screening in high-risk patients (26).
- For planning and monitoring the effects of neoadjuvant treatment (27).
- For planning partial breast irradiation (PBI).
- To examine the integrity of a breast implant, to look for implant rupture (especially if physical signs are present), if the result of this examination will influence the treatment.

Important note: In premenopause, contrast-enhanced breast MRI should be performed at week 2 or possibly week 3 of the cycle, otherwise the false positive rate will be very high.

Contraindications for Breast MRI

- General contraindications for MRI (e.g., pacemaker, etc.)
- Nonspecific clinical symptoms (e.g., breast pain) with negative mammography and ultrasonography results.
- MRI should not be used instead of biopsy for lesions that can be evaluated only pathologically, e.g., to characterize microcalcification.

Relative Contraindications for Breast MRI

- Due to a limited evaluability, it is generally not recommended for 6 months after surgery and within 12–18 months after radiation therapy, except for special cases (and only after prior consultation with a radiologist).
- After a core/vacuum-assisted biopsy, there is no need to wait before MRI scanning, but if possible, it is recommended that it should be delayed for a couple of weeks: it is advisable to wait for any haematoma to be absorbed, although this does not usually interfere with diagnosis.
- Metal clips inserted during surgical or radiological intervention do not interfere with breast MRI; however, the filling valve of some expander implants may make scanning impossible due to their ferromagnetic material.
- Pregnancy (see below).

Important note: By default, MRI is not required for implanted breasts for either screening or diagnostic purposes.

Breast MRI Is Not Indicated

- For histological characterization in cases where a targeted biopsy can be performed (differentiation of scar site recurrence, for characterizing microcalcifications, nodules of unknown nature, etc.)
- In the event of uncertain cytological examination with non-informative (C1) or borderline (C3) results (in such cases a core biopsy should be performed).
- For the accurate evaluation of axillary lymph nodes.
- Instead of mammography, if the patient has radiophobia.
- For routine follow-up of operated, treated patients instead of mammography or ultrasound.

Promising Breast MRI Indications Still Under Investigation

- Examination of discharging breasts and to support therapeutic decision-making for B3 lesions (24).
- A large multi-centre study (Preoperative Breast MRI in Clinical Practice: Multicenter International Prospective Meta-Analysis [MIPA] of Individual Data) is ongoing to demonstrate that a breast MRI scan would be required before treating any confirmed tumour. Several studies have found that preoperative MRI modifies therapy by 15%–25%, but their statistical power is not yet sufficient to make this recommendation general (25).
- MRI spectroscopy is still in the research phase. This special procedure may increase the specificity of assays by detecting a tumour-specific component (e.g., a choline peak).

Ductography (Galactography)

Ductography may be used when an intraductal process is clinically suspected if this cannot be excluded by other imaging and intervention methods. It can also be used for dye marking of affected ducts before surgery. Because of its low sensitivity and specificity, it is not suitable for excluding an intraductal process in the event of a negative result. In some countries (e.g., the United Kingdom) it has been removed from the list of interventions used in practice. MRI has started to take over the role of ductography. Based on a large review study, the sensitivity and specificity of MRI (92% and 97%, respectively) for carcinomas are significantly higher than for galactography in the diagnosis of patients with discharging breasts. In the event of negative mammography and ultrasound results, MRI scanning is recommended as a next step of assessment (28).

F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

- Not suitable for breast screening (29–38).
- If breast cancer is suspected, routine testing is not justified because of its low sensitivity in the detection of tumours that are
  - Less than 5 mm in diameter and
  - Those with low FDG avidity (DCIS, LCIS, low-grade lobular carcinoma, tubular carcinoma)
- PET/CT is less suitable than breast MRI for searching for occult breast tumour.
- 18F-NaF PET/CT may be chosen as an alternative to conventional bone scintigraphy (not yet reimbursed in Hungary).

Positron Emission Mammography

Positron emission mammography alone is not suitable for breast screening. PEM is a dedicated breast camera with a resolution of 1–2 mm that can be used as a complementary method to mammography and breast ultrasound. It is primarily recommended in patients in whom MRI scanning is not indicated or not feasible for any reason. Its sensitivity and specificity in the identification of malignant foci within the breast are nearly identical to those of MRI. It can be used to determine multiplicity within the breast, to differentiate scar and tumour in an operated breast, and to measure response to chemotherapy. Stereotactic sampling systems used in mammography can also be used for PEM (device dependent). When using the method, radiation exposure (3.0–3.5 mSv) to the radiopharmaceutical used (which is not focused to the breast) should be taken into account (39). Not available in Hungary.

Positron Emission Tomography/Magnetic Resonance Imaging

PET/MRI is a promising technique that is still primarily used for research; its use is recommended in patients for whom PET and MRI indications coexist and minimization of radiation exposure is essential (40, 41).

INTERVENTIONAL PROCEDURES

The result of preoperative/pre-therapeutic complex diagnostics should provide sufficient certainty for the operating surgeon to plan the surgery accurately and/or for the oncologist to choose the therapy.

In the event of a positive (malignant) aspiration cytology (FNA) result, a consensus must be reached between the pathologist, oncologist, surgeon, radiologist and the patient when establishing the indication for surgery/therapy, along with a correlation between the radiological and pathological results.

Breast screening and diagnostic study sites should provide the opportunity (or a background in another facility) for guided sampling for all imaging procedures (mammography, ultrasonography). (MRI-guided intervention is currently not available in Hungary.) For an image-guided intervention, it should be documented through images that the device has reached the lesion and sampling conditions (target description, exact location [quadrant/clock face/distance from nipples/fold], device, targeting, validation, clip position) must be recorded.

Efforts should be taken to obtain a definitive diagnosis from the first sampling, and there should in any case be no more than

two samplings. To do this, an appropriate sampling and guiding type should be chosen.

Guiding Biopsy

Sampling should always be guided by an imaging technique, for both palpable and non-palpable lesions.

- Ultrasound-guided sampling of the breast and regional lymph nodes is recommended if the palpable or non-palpable lesion is clearly visible on ultrasound.

It is strongly contraindicated that after an ultrasound-guided sampling with a benign result. Lesions which are not well identifiable by ultrasound are followed-up only.

- Mammography-guided (stereotactic) sampling is required for non-palpable, non-ultrasound-identifiable lesions that are not certainly benign, e.g., microcalcifications. Aiming can be done in a sitting/lying/or side lying position. Lesions visible only on tomosynthesis (mostly structural distortions) may only be aimed at by tomosynthetic stereotaxis (which cannot be replaced by MRI). The latter method is not currently funded by the NEAK (National Health Insurance Fund of Hungary).
- MRI-guided sampling (42) is performed when a uncertain or suspicious lesion detected by contrast enhanced MRI, not visualized by mammography or ultrasound, a decision cannot be made as to whether the lesion is benign or malignant. Sampling should be performed in a vacuum-assisted manner, and a marker clip should be inserted after the procedure.

Biopsy Tools—Aspiration Cytology, Core Biopsy, Vacuum-Assisted Biopsy

Fine needle aspiration cytology (FNA, FNAB, FNAC), core biopsy, and VAB are all extremely important in diagnosis and therapeutic planning. Cytology is a faster, cheaper, but more inaccurate procedure (more false negatives and non-evaluable specimens), while core biopsy is more accurate (histological type, immunohistochemical parameters, definitive confirmation of benignity), and usually eliminates errors in evaluating fibrotic lesions and lesions in treated breasts. Because of the low reliability of FNA, it is contraindicated in some countries for breast diagnostics—except for evaluation of fluid-containing structures.

In some cases, VAB is the first choice of method according to current recommendations.

Detailed, state-of-the-art professional recommendations and possibly local availability should be considered when choosing a biopsy procedure (device/needle), except for the following cases:

- Vacuum-assisted biopsy (VAB) (43) is the gold standard for evaluating microcalcifications, but in selected cases (lesions larger than 10 mm, etc.) a conventional core biopsy may be sufficient. FNA is not suitable for the diagnosis of calcifications, partly since the effectiveness of sampling (presence of calcification in the sample) cannot be validated.
- In order to validate the biopsy of calcifications, specimen mammography of the tissue cylinder is mandatory; the presence of calcifications must be stated in the biopsy report. If calcification cannot be visualized within the tissue cylinder on specimen mammography, sampling (in the event of a negative result) cannot be considered representative, and therefore a therapeutic or follow-up decision cannot be made based on this.
- If FNAB is performed in an atypical lesion or a lesion suspected of malignancy (RKU 3, 4, 5, BI-RADS 4, 5), a negative or benign cytology result cannot be accepted to rule out malignancy, when a benign lesion diagnosed on FNA (C2) is not clearly stated or if the radiopathological correlation is questionable or it is not seen.
- If for any lesion, proper information cannot be obtained for therapeutic decision-making using repeated, adequate sampling with a higher-level biopsy method, surgical excision may be required.
- Core biopsy should be performed in all cases when it is requested for therapeutic planning or by protocols of other disciplines (surgery, oncology) (e.g., for neoadjuvant treatment, mastectomy, axillary dissection).
- Default needle size for core biopsy: 14G. In case of suspected carcinoma insitu/microcalcifications, the use of a needle sized 12G is recommended; default needle size for vacuum-assisted biopsy: 7G–9G.
- None of the sampling procedures is suitable for definitive diagnosis in papillary lesions, ADH and some other B3/C3 cases, which require surgical or vacuum-assisted excision and complete histological processing. In the event of an insitu carcinoma, none of the sampling methods is suitable to rule out a possible invasion.
- For cytology from a lesion in any tissue type (except lymph nodes) that fails or has uncertain results, core biopsy is usually required, and not repeat cytology.
- In the event of a failed core biopsy (for non-technical reasons), vacuum-assisted sampling should be considered instead of a repeated core biopsy.
- If the need for sampling has already been stated for a lesion (i.e., the suspicion of malignancy has arisen with any probability), follow-up cannot be recommended without establishing a specific diagnosis (e.g., for a C1 result).
- During preoperative diagnostics, an abnormal radiological lesion may be completely removed, and in such cases placement of a marker clip is imperative.

ALGORITHMS FOR ASSESSMENT

Screening for Breast Cancer

Organized public health screening: a nationally organized invitation-based screening programme for women with a medium risk aged 45–65, every 2 years in Hungary (other countries: see **Table 1**) (1, 2, 44–52). (A public health programme initiated by the health care system as a provider, publicly funded or involving population groups considered to be

TABLE 1 | Timelines of breast-screening programmes with age covered in studied countries by Central and Eastern European Academy of Oncology as reported by panel members.

Country	Implementation of screening programmes	Age covered
Armenia	Pilot 2021–2023 in 3 of 11 regions of the country	50–69
Azerbaijan	2008	30–70
Bulgaria	2012	45–69
Georgia	2008	40–70
Hungary	2001–2002	45–65 (soon will be modified to 40–75)
Kazakhstan	2008	40–70
Poland	2006	50–69
Russian Federation	2006	40–75
Romania	2008	50–69
Serbia	2012/13	50–69
Slovakia	2019	50–69

at risk, implemented with a professionally justified frequency.) (53).

Individual (opportunistic) screening: occasional imaging studies of women over the age of 40 years at average risk, with no symptoms suggestive of tumour, no history of breast cancer, for ruling out breast cancer. (Occasional use of methods suitable for recognizing a hidden target condition, related to other medical activities or spontaneously required.)

Assessment methods:

- Physical examination + mammography (medical technician).
- Evaluation of mammography: double medical reading (radiologist).
- In case of positive or doubtful results, the patient should be recalled for a complex diagnostic breast assessment (additional investigations), which is needed to clarify the issue: targeted, zoomed, etc. images, ultrasound scanning, guided sampling, MRI, etc.

Screening of high-risk women (26, 54–59): mutations in the currently known "breast cancer genes" explain 25%–30% of familial breast cancers; other predisposing genes are still unknown. Detection of missing genetic heritability is a central theme of current research (60, 61). Based on this knowledge, it is considered important that in cases of confirmed familial breast or ovarian cancer BRCA1,2 mutation, Li–Fraumeni syndrome, Bannayan–Riley–Ruvalcaba syndrome, Cowden syndrome, Peutz–Jeghers syndrome, and a history of chest radiation administered 10–30 years previously, screening recommendations should also apply to individuals with a breast cancer risk above 20%–25% according to validated mathematical tests. Among mathematical models, the best known are: BRCAPRO, BOADICEA, modified BOADICEA, (2008) Gail, Claus, Tyrer-Cuzick, Myriad I/II and COUCH models. It is advisable to use models that also take into account an extended family history. It should be noted that the National Institute of Health and Care Excellence (NICE) in the UK recommends the use of BOADICEA to decide whether to carry out MRI screening of high-risk patients (62).

Screening recommendation in Hungary for the high-risk group: Above the age of 30 years, mammography (2D digital mammography, or possibly with 3D tomosynthesis and 2D synthetic software) and ultrasound scanning, complemented by annual MRI (when possible), is recommended: at least from the age of 30 years for known BRCA1/2 carriers, and at least from the age of 20 years for those with TP53 mutations (35). Omitting use of mammography screening has to be considered at patients with Li-Fraumeni syndrome, due to the risk of secondary radio-induced malignancies (63).

Hormonal induction (*in vitro* fertilization programme): Most data in the literature do not support an increased risk of breast cancer after fertility-enhancing hormone treatments, although there is always a theoretical chance of this occurring. Based on individual judgement (mainly after repeated or long-term treatments), annual mammography screening should be considered in women undergoing such treatment (64).

Diagnostic (Clinical, Complex) Breast Assessment

Detailed assessment and individualized screening of patients who have complaints, and of those revealed by screening. The purpose is to establish a maximally accurate preoperative/pre-therapeutic (non-operative) diagnosis (preferably complemented by cytology/histology sampling) in order to optimize the malignant/benign ratio for cases undergoing surgery. According to EU protocol indicators, at least 90% of cases of confirmed malignancy require a preoperative biopsy at the time of diagnosis (35, 65, 66).

In terms of workforce, the recommendation is that all steps of complex breast diagnostics be performed by either one radiologist or as few radiologists as possible, so the diagnosis, based on information provided by each modality and interventions will be as accurate as possible.

Referral to mammography/ultrasonography: since the choice and feasibility of imaging methods required for an individual patient depend on several factors (clinical questions, age, breast size, etc.), it is recommended that the patient be referred for "complex breast assessment" instead of "mammography" and

"breast ultrasound", and the investigating physician should decide what investigations they consider necessary, depending on the clinical question.

Above the age of 30–35 years (age limit should be determined on an individual basis and is the competence of the radiologist):

- Physical examination (physician or certified nurse) + mammography (medical technician).
- Evaluation of mammography: single medical reading (radiologist).
- Additional ultrasound scanning (evaluation by the radiologist): palpable, circumscribed lesion, hyperdensity, discharging, inflammatory, operated, implanted, non-involutional, dense breasts with a complex mammographic structure, in cases of high risk, etc. (67).
- Sampling, if necessary.
- It is recommended that a breast MRI be performed if mammography, ultrasound and sampling did not provide enough information, but only when confirmation of diagnosis by MRI can be expected (and only based on a preliminary radiological consultation).

Under the age of 30–35 years (age limit should be determined on an individual basis and is the competence of the radiologist):

- Physical examination (physician or certified nurse) and ultrasound scanning (67).
- Evaluation of ultrasound scan: single medical reading (radiologist).
- Mammography, if needed (women who have given birth, for large breasts, in high-risk cases, in individual cases, etc.) with a single reading (radiologist).
- Sampling, MRI, etc., if needed: see the previous paragraph.

Follow-Up of Lesions

Follow-up over time is sufficient only for lesions with a radiomorphology showing a probability of malignancy of less than 2% (BI-RADS category 2 or 3, or stable condition documented for at least 3 years, for solid lesions). If the probability is 2% or more and in the absence of a follow-up history, sampling is mandatory (23). Depending on the type of lesion, follow-up is usually performed in 6-month cycles, for up to 3 years. For inflammatory processes, follow-up in shorter cycles may be justified.

ARTIFICIAL INTELLIGENCE IN BREAST DIAGNOSTICS AND SCREENING

The task of artificial intelligence (AI) is to implement human intelligence using computational models. The goal is to make computers capable of performing tasks that can be accomplished by human intelligence. Artificial intelligence is a system that displays intelligent behaviour, analyses its environment, and is able to act with a certain degree of autonomy to achieve a specific goal (68). Artificial intelligence is based on machine learning rather than on conventional computer programming. During this process, the computer is provided with a set of data and expected responses, after which the machine will create the rules. Based on the established rules, the machine itself will provide the answers based on new data. This also means that during the learning phase, it is worth using as much data as possible and that such systems are capable of continuous improvement. Radiology finds itself in a special situation also because, owing to digital image archiving systems that became widespread years ago, a huge database is now available, constituting a basis for such developments.

The CAD (computer-aided detection) systems used in the early 2000s were based on conventional programming. After initially promising results, these systems did not become widespread in everyday practice. The performance of the film reader radiologist did not improve, the number of recalls increased, but the rate of tumour detection did not improve (69, 70).

Artificial intelligence based on machine learning seems to be a promising development, with many studies showing encouraging results in reading mammograms captured on various devices, and many results show accuracy similar to human performance under research conditions (71–73).

Assessing breast density is important in many ways (diagnostic difficulty, medico-legal problems, individual risk). As a best practice, description of breast density in radiology reports is increasingly frequent; however, evaluation of this feature shows significant inter-observer differences. There are currently multiple breast density analysis systems on the market that have been approved by the FDA (74–76).

With the spread of digital tomosynthesis, the amount of information and time required for reading continues to grow, which further increases the need to find new solutions. Evaluation of image material generated during automated ultrasound scanning is another direction of development. Breast MRI scans have also attracted the interest of artificial intelligence development groups and companies (77). Evaluating the response to neoadjuvant treatment seems to be a promising area within this. Development of decision-making algorithms is also expected to receive a boost.

Currently, only recommendations based on limited evidence can be formulated. It is difficult to compare different studies, and a standardized method for comparison of studies and efficacy has not yet been established. At present, solutions based on artificial intelligence are not yet applicable in daily routine patient care (78). Results are expected in the following applications (79, 80):

- Assessment of breast density, individualized risk assessment.
- A combination of a radiologist and AI instead of a double reading.
- Highly reliable negative mammography reading by AI (without human intervention).
- Other imaging techniques and AI.
- Clinical decision support systems.

ASSESSMENT PROTOCOLS

Assessment of a Discharging Breast

- Physical examination—to be documented: colour, side, amount of discharge, whether it is spontaneous or appears on compression, number or possible localization of discharging ducts, duration (onset, continuous or intermittent, nature of change), other symptoms (e.g., inflammation) and whether the discharge is pathological (28).
- Non-pathological discharge: unilateral/bilateral discharge from multiple ducts.
  - Actions: mammography (over 30–35 years) and ultrasound (under 30–35 years only ultrasound), discharge (contact) cytology (at onset).
  - If these investigations have negative results, no further diagnostic actions are needed.
- Pathological discharge: bloody, serous or colourless discharge from one duct (especially if unilateral), usually spontaneous and persistent.
  - Actions: mammography (over 30–35 years), ultrasound, discharge cytology.
  - In 35%–56% of cases, this is caused by papilloma or duct ectasia, and by DCIS or IDC in 5%–23% of cases. If image is suggestive of intraductal papillary lesion or DCIS, IDC, assessment should be continued according to guidelines for solid structures or malignancy.
- If mammography and ultrasound scanning show negative results and blood or other signs of epithelial proliferation are found in the discharge on cytology examination, MRI or galactography may clarify the cause of the discharge, and location, multiplicity, and extent of underlying lesion(s). Of the two modalities, MRI is preferred because of its higher sensitivity and higher specificity.
- If either method yields positive results, it is recommended that ultrasound scanning be repeated and mammography re-evaluated, or possibly that additional images be captured to reveal the lesion. If a lesion is identified, a core biopsy is required.
- If the clinical picture and discharge cytology are positive, but imaging modalities do not identify any cause for the discharge, surgical retromammillary cone excision may be performed.

Assessment of Benign Solid Lesions

In K2, U2 (BI-RADS 2–3) cases, patient at normal risk (no multiple positive family history or confirmed gene mutation), with a sharp-edged, ovoid lesion not larger than 3 cm, having homogeneous structure and a longitudinal axis parallel to the skin surface, containing less than four (macro) lobulations, and displaying no hyperechoic halo sign (81–84).

- Physical examination
- Ultrasound scanning under the age of 30–35 years, complemented by mammography, if needed (suspected malignancy).
- Mammography over the age of 30–35 years, additional scans, when needed.
- Ultrasound scanning at all ages.
- Sampling: not recommended under the age of 25 years; to be considered between 25 and 30 years; strongly recommended over the age of 30 (except for unequivocal lesions such as fat necrosis, intramammary lymph node, lipoma, hamartoma).

Core biopsy is the preferred method. If, however, for any reason, cytology is performed and yields a C2 result but the report does not clearly state a definite diagnosis (e.g., fibroadenoma) the result is not acceptable. For a growing lesion, or if lesion diameter is greater than 3 cm, a core biopsy is recommended.

- If an increase in diameter of more than 20% is observed within 6 months, a core biopsy is mandatory and surgical excision should also be considered, due to the suspicion of a phyllodes tumour (85).
- For a multifocal process, sampling is recommended from the largest and/or least regular lesion.
- At any age: if no sampling is performed, follow-up is recommended every 6 months for at least 1 year; If it does not grow during this time, there is no need for follow-up.
- Biopsy is not required for macrocalcification characteristic of fibroadenoma (popcorn calcification).
- For multifocal lesions, MRI scanning for more accurate follow-up or for surgical planning is recommended.
- Cryoablation may only be performed when there is a core biopsy report (86).

Assessment of Solid Lesions (BI-RADS 4–5) With Malignant (R5, U5), Suspected Malignant (R4, U4) or Uncertain Appearance (R3, U3)

- Physical examination (86–88).
- If a strong suspicion of malignancy arises, mammography is mandatory at all ages (including patients aged under 30) (to assess the DCIS component, etc.), with additional images, if needed.
- Ultrasound scanning (breasts + axillae) is mandatory at all ages.
- Sampling is always mandatory. Core biopsy is the preferred method and is unavoidable if a suspicion of malignancy arises on physical examination or diagnostic imaging. If, however, cytology is performed with a C1-C2-C3 finding, the result is not acceptable for excluding malignancy, in which case a core biopsy is mandatory.
- For an ultrasound-positive axilla, sampling is mandatory (cytology or core biopsy).
- For a multifocal process, if foci are not in close proximity to each other, sampling should be performed from the two furthest foci.

- For multifocal processes, preoperative MRI scanning is recommended to assess extent, especially for DCIS-associated carcinomas and lobular carcinomas.

Assessment of Complicated Cysts

- Physical examination (11).
- Ultrasound scanning in patients under 30–35 years of age.
- Mammography in patients aged over 30–35, with additional images and ultrasound scanning, if requested.
- Doppler examination of content (growth), possibly examination of its mobility by changing body position.
- For mobile contents (i.e., clot/dense fluid) no sampling is requested for diagnostic purposes, if the cyst otherwise has a regular shape.
- Ultrasound-guided aspiration cytology of cyst fluid, and cytology or core biopsy of the solid part.
- Assessment of growth mobility with needle during sampling.
- If cyst is emptied, it is recommended that a marker clip be placed after sampling, though this is difficult to do, as this device is not currently reimbursed.
- Note: in patients aged over 30, if only one cystic structure larger than 10 mm is visible or develops in the breasts, even if it has a regular morphology, sampling should be considered due to the possibility of medullary/mucinous carcinoma/lymphoma/metastasis.

Assessment of Calcifications

- For the analysis of questionable calcifications seen on a mammographic image, targeted zoomed or open zoomed images are suitable; there may also be a great need for these in digital mammography or synthetic 2D images (23, 89, 90).
- No sampling is indicated in cases of non-clustered, saucer-like microcalcifications with transparent centres located in the skin or just subcutaneously, or for macrocalcifications.
- With MRI scanning, the nature of the calcification cannot be defined with complete certainty; MRI therefore does not replace biopsy, and it is usually not indicated for characterization.
- Stereotactic, vacuum-assisted biopsy (VAB) is the preferred method in most cases (43). Above a diameter of 10 mm, a 12 (14)G core biopsy may also be performed, but its effectiveness (rate of non-evaluable samples, upgrade rate in final histology) is lower compared to vacuum-assisted sampling.
- If mammography of the biopsy specimen (core specimen) does not confirm any calcification, the biopsy cannot be considered representative, and a negative result, despite the calcifications described in the histological report, is not acceptable. In such cases, no therapeutic decision can be made, and follow-up alone cannot be recommended. Sampling should be repeated (mainly by vacuum-assisted method).
- If stereotaxis is not available or is available only with considerable delay, or if calcification is associated with a palpable or solid lesion identifiable on ultrasound scanning, then an ultrasound-guided core biopsy should be performed. If on mammography calcification was confirmed within the sample (core specimen), a radiopathological correlation is present, and a negative result is acceptable. In the presence of calcifications, FNA is not a suitable procedure.
- After sampling, it is recommended that marker clips be placed to identify the biopsy site and to facilitate any subsequent preoperative marking.
- For DCIS/EIC, preoperative MRI is recommended to clarify the extent of the lesion (91).

Assessment of Architectural Distortions

- Physical examination: radial scar/complex sclerosing lesion is almost never palpable, no skin thickening/retraction is seen.
- If mammography shows architectural distortion in at least one view, additional images are required (i.e., several aspects: targeted compression without zooming, or targeted zoomed, tomosynthesis, when possible) (23, 90).
- If it can be reliably identified by ultrasound, a core biopsy or VAB with this kind of guiding, if not identifiable, then stereotactic guidance is required.
- After sampling, it is recommended that marker clips be placed to identify the biopsy site and to facilitate any subsequent preoperative marking.
- The previously used "white/black star" mammographic morphological markers are unreliable for differentiation between a tumour and a radial scar, since there are overlaps in both directions.
- MRI may help with characterization, but it does not unequivocally establish the nature of the lesion and it, therefore, cannot replace biopsy.
- If architectural distortion is only visible on tomosynthesis, conventional (2D) stereotactic guidance is not suitable for aiming, and only 3D tomosynthesis-driven stereotaxis will be adequate for this purpose. In such cases, MRI cannot replace biopsy.
- FNA is not suitable for characterizing these lesions.
- When large distortions are encountered, MRI scanning may be recommended in all cases with negative histological results, and to assess the exact extent for cases with positive histology results.

Assessment of Asymmetric Hyperdensities

- Physical examination, careful medical history (prior surgery, etc) (23, 90).
- Mammography with multidirectional complementary images (zoomed, tomosynthesis), if needed, followed by MRI/stereotaxis if a suspicion still remains.
- Ultrasound scanning.
- If ultrasound gives negative results, an MRI should be considered, especially if a palpable/clinical abnormality is found.
- Sampling is recommended (primarily core biopsy) for any type of circumscribed abnormality found on ultrasound.

- Sampling (core biopsy or cytology) is recommended without image-guided aiming if there is a negative ultrasound but a suspicious palpable abnormality.

Assessment of Nipple and Areolar Wounds

- Physical examination, medical history (92).
- Ultrasound scanning for patients aged under 30–35 years, but in cases of suspected malignancy, mammography should also be performed.
- In patients aged over 30–35 years: mammography, ultrasound scanning.
- Initiation of a dermatological consultation.
- Abrasion cytology sampling, indicating or performing a surgical biopsy (punch biopsy) of the wound located at the surface of the nipple/areola.
- If calcification suggestive (even only slightly) of malignancy is seen in the breast, a stereotactic biopsy is recommended.
- If on ultrasonography, a circumscribed dilated duct or a solid structure is detected, an ultrasound-guided core biopsy or possibly cytology is recommended.
- If mammography and ultrasound scanning have negative results, and nothing abnormal is revealed on dermatological consultation, but the lesion persists for a long time, MRI examination should be considered.
- If nipple biopsy is positive for tumour, an MRI scan should be considered to evaluate the extent.

Assessment of Suspected Inflammatory Breast Cancer

- Physical examination, medical history.
- Mammography, ultrasonography.
- If pathological axillary lymph nodes are seen, they should be sampled for cytology or core biopsy.
- In the absence of abnormal lymph nodes and of detectable masses in the breast, ultrasound-guided puncture of the dilated lymphatic vessels for cytological examination may help in establishing a diagnosis.
- An ultrasound-guided core biopsy should be performed from any suspicious circumscribed area seen on ultrasound scanning.
- MRI scanning, and targeted biopsy of any detected circumscribed lesion.

Assessment of Abnormal Axillary Lymph Nodes

- In cases of multiple axillary adenopathy, number and size range of lymph nodes showing abnormal morphology should be stated in the radiology report.
- For a known malignant lesion in the breast, FNA may be sufficient to confirm axillary metastasis.
- If mammography and ultrasound show nothing abnormal in the breast, core biopsy of the axillary lesion is preferred.
- If biopsy raises the possibility of breast origin, an MRI scan is recommended to look for an occult tumour.

Radiological Procedures for Malignancies/ Suspected Malignancies

For Surgery

- Preoperative marking of non-palpable breast lesions: non-palpable breast tumours are operated after preoperative localization. The lesion should be marked with ultrasound, mammography, MRI, wire hook or radionuclide (liquid or needle [seed]) (radioguided occult lesion localization, ROLL) (93, 94) guided techniques, sometimes with dye (e.g., when filling a discharging duct). The use of MRI control is justified when a lesion can only be visualized on MRI or when its extent cannot be unequivocally defined on conventional imaging.
- Combined radionuclide preoperative labelling and sentinel lymph node labelling (SNOLL) are also increasingly commonly used techniques.
- For preoperative localization, 2-view intraoperative specimen mammography or 3D tomosynthesis or specimen ultrasound is mandatory (95). A radiological report should be prepared, containing information about the presence of the abnormal lesion, the marker clip and the marking wire, and about the radiological involvement of margins.
- Sentinel lymph node biopsy (SLNB): If no metastatic lymph node is confirmed in the axilla during preoperative assessment, the sentinel lymph node should be removed as part of staging. Sentinel lymph node(s) is/are the "first" lymph node(s) on the lymphatic drainage pathway of the tumour where lymphogenous metastasis may initially develop. It/they can most effectively be identified with a combination of ^{99m}Tc nanocolloid and patent blue. If there is a palpable abnormality and mastectomy is performed, the radiopharmaceutical (marker) is administered periareolarly; the radionuclide is administered by a nuclear medicine specialist and patent blue by the surgeon. If the sentinel lymph node is tumour-free, then the other lymph nodes in the axilla are also likely to be so (96).
- Preoperative localization of extensive microcalcifications (DCIS) and radial scar is recommended primarily with hookwire(s); for other lesions the radioactive localization method is more advantageous (97, 98).
- For non-palpable lesions, radioactive or magnetic labelling seeds are forward-looking approaches that can be used for labelling of both the breast and the axilla (99, 100).

For Neoadjuvant/Primary Systemic Treatment

- Effectiveness of neoadjuvant therapy should be monitored using appropriate imaging studies (mammography, ultrasound, breast MRI).
- For a dense breast structure, MRI scanning is the recommended method. Breast MRI shows most accurately the extent of the residual tumour and structural and size changes following treatment.
- For a good regression (downstaging) of a breast tumour (ideally at the start of any neoadjuvant treatment), an MRI-compatible metal marker should be placed in the breast

TABLE 2 | Care protocol for B3 lesions based on the "Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions)".

	If diagnosed by core biopsy	If diagnosed by vacuum-assisted biopsy (VAB)
ADH	Surgical removal	Surgical excision, in some cases follow-up based on the decision of the oncology team
FEA	Lesions detectable on diagnostic imaging, VAE recommended	Follow-up if the lesion detectable on diagnostic imaging has been completely removed
LN	Surgical removal or VAE (removal of a lesion visible on ultrasound scanning)	Surgical excision or follow-up appropriate for high-risk lesions if the lesion detectable on diagnostic imaging has been completely removed
PL	VAE is recommended	Follow-up if the lesion detectable on diagnostic imaging has been completely removed
PT	Surgical removal, negative surgical margin is required for borderline and malignant PT	Follow-up if the lesion detectable on diagnostic imaging has been completely removed for a benign PT
RS	VAE or surgical removal of a lesion detectable on diagnostic imaging	Follow-up if the lesion detectable on diagnostic imaging has been completely removed

ADH, temporary diagnosis corresponding to atypical ductal hyperplasia, which can only take into account the dimension seen in the biopsy sample; FEA, flat epithelial atypia; LN, classical lobular neoplasia; PL, papillary lesion; PT, phyllodes tumour; RS, radial scar; VAE, vacuum-assisted excision.

tumour under image guidance, if breast-conserving surgery is possible. This kind of preoperative localization can also be performed in cases of full regression. Surgical criterion is an intact surgical margin, the achievement of which is supported by an imaging examination—preoperative breast MRI scanning (101).

- If required, a lymph node that is considered to be metastatic can be clip marked after sampling; thus, selective removal (targeted axillary sampling [TAS]) of the lymph node in question can be performed and pathological assessment of nodal regression improved.

Image-Guided Minimally Invasive Tumour Ablation

- A promising technique for breast cancer is focused ultrasound (FUS, HIFU), a method that can be used with both ultrasound and MRI guidance. Ablation success ranges from 20% to 100%, depending on the type of the FUS system, imaging technique, ablation protocol, and patient selection (102).
- Cryotherapy is an accepted (FDA approved) method in benign cases (for histological biopsy diagnosis of fibroadenoma) (103–105). In Hungary, it is not funded by the NEAK (National Health Insurance Fund of Hungary).
- It is also a promising alternative in selected cases of malignancy and is already a subject of studies (106). A completed phase II study confirmed successful ablation in 76% of cases (107–109).
- Based on the results so far, radiofrequency ablation can be used successfully in elderly patients for whom surgery is not feasible, except for lobular carcinoma. This is not yet a practice in Hungary (110–112).
- Diagnostic image-guided vacuum-assisted excision of B3 lesions. Percutaneous, image-guided diagnostic vacuum-assisted excision has been becoming a practice in the care of smaller B3 lesions (69). Its purpose is to remove the entire lesion without surgery, usually up to a size limit of 20 mm. It is especially suitable for papillary lesions without atypia, radial scars, FEA, AEPDT, classical lobular neoplasia and mucocellular lesions. It may be indicated by the oncology team. MRI scanning may help to preclude malignancy (113, 114).

Therapeutic Algorithm for B3 lesions

- Lesions with uncertain malignant potential (B3 lesions) represent an extremely heterogeneous group with a 9.9–35.1% risk of developing a malignant process (115–117).
- The current protocol for the treatment of B3 lesions was discussed at international consensus conferences in Zurich in 2016 and 2018. The latest recommendation 2020 on processing B3 lesions states that a multidisciplinary (oncology) team should provide an opinion on each B3 lesion.
- The recommendations for the treatment of B3 lesions after histological diagnosis are:
  - follow-up (mammography and/or ultrasound scanning every 6 months or annually, depending on diagnostic imaging reports).
  - vacuum-assisted removal.
  - surgical excision.

Table 2 presents the care protocol based on the "Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions)". **Table 3** shows proposed treatments for the most common lesions under the NHS (UK) protocol.

Screening, Diagnostics and Follow-Up of Breasts That Have Undergone Cosmetic Surgery

Before cosmetic surgery (implantation, reduction, etc.): an age-appropriate imaging study should be performed to rule out a space-occupying process.

After breast augmentation for cosmetic reasons: age-appropriate screening/diagnostic tests; the same as for the normal population: mammography (with modified technique for implants: Eklund views, if technically possible), ultrasound scanning and, if necessary, guided sampling. MRI is not required by default for implanted breasts for either screening

TABLE 3 | Management protocol for B3 lesions based on NHS (UK) protocol.

Diagnosis with core biopsy (14G) or VAB	Therapeutic recommendation
Radial scar with epithelial atypia	VAE recommended, removal of 12 × 7G tissue cylinders
Papillary lesion with epithelial atypia	Surgical excision
Mucocele-like lesions with epithelial atypia	VAE recommended, removal of 12 × 7G tissue cylinders
Cellular fibroepithelial lesion	Surgical excision

VAB, vacuum-assisted biopsy; VAE, vacuum-assisted excision.

or diagnostic purposes. The most accurate method for assessing implant integrity is breast MRI. MRI scanning is also the most suitable method when imaging of the space behind the implant is required, but this is considered only in exceptional indications. Axillary silicone lymphadenopathy can be detected reliably by ultrasound, but for the assessment of other lymphatic regions (internal mammary), MRI is the suitable method.

Breast Implant-Associated Anaplastic Large Cell Lymphoma

The association between ALCL and breast implants with a textured surface was first suspected in 1996, with current statistics suggesting that it may occur yearly in 0.3–1/1 million women with breast implants (118). According to the literature, it is likely that there is a rare association between breast implants and the development of anaplastic large cell lymphoma, but further data is needed. BIA-LCL may be suspected 7–10 years on average after implantation, in the presence of a unilateral, increasing fluid accumulation. In such cases, cytological, bacteriological and CD30 testing of the fluid is required, and when soft tissue lesions are also present, core biopsy and MRI scanning should be considered.

Assessment of Male Breasts

In the event of symptoms, the male breast assessment algorithm is the same as for the female breast. If a breast cancer is present, follow-up after treatment is also the same as for the female breast. Ultrasound scanning is sufficient for instrumental examination of pubertal gynaecomastia. When examining gynaecomastia in adults over the age of 30, mammography should also be performed, complemented by sampling, in doubtful cases.

Breast screening is not required in men without symptoms. Some recommendations suggest regular mammography screening for men at high risk for breast cancer (e.g., carrying BRCA gene mutation) (119–121).

Gestational Breast Cancer

Breast cancer revealed during pregnancy or within 1 year after delivery is called gestational breast cancer.

Breast Assessment in Pregnant Women

Ultrasound is the primary modality for assessing a pregnant woman's breast complaint. If necessary (e.g., suspected tumour, DCIS/EIC component, etc.) mammography can be performed observing radiation protection guidelines. Breast MRI is more difficult due to the necessity for contrast medium, as well as the increased abdominal circumference and prone position during the scan. Generally, administration of MRI contrast medium during pregnancy is a relative contraindication, but most of the contrast media approved for use in Hungary can be applied "if the clinical status of the woman necessitates it". There are significant differences between countries and types of contrast media, so local pharmaceutical regulations should always be followed (35).

The assessment algorithm for a lactating breast is the same as for a non-lactating breast (122).

TABLE 4 | RKU coding of lesions.

1	Non-pathological (negative)
2	Benign
3	Indeterminate (uncertain benign/malignant)
4	Suspicious of malignancy
5	Clearly malignant

R, radiology = mammography; K, clinical/physical examination; U, ultrasound scanning.

Coding

- For multidisciplinary cooperation, it is desirable to use the following codes in radiology reports: R (1–5), K (1–5), U (1–5). The BI-RADS (0–6) code can also be entered as an option. It should be clearly indicated whether the coding is according to RKU or BI-RADS (**Table 4**, **5**). If the two sides are not identical, the code should be entered separately (right, left) (23).
- Standardized coding facilitates clear communication between physicians. Some countries in Europe use the same system as Hungary, but the BI-RADS (Breast Imaging Reporting and Data System) scheme is internationally known and the most widespread.
- The BI-RADS system also provides precise guidance on the content of radiology reports, providing a uniform format for:
  - Indication for the investigation (screening, clinical study, follow-up; history data).
  - Type of breast structure (see **Tables 6**, **7**).
  - Description of abnormalities in the breast (solid structure, asymmetry, structural disorder, calcification, abnormalities associated with the pathological process: skin thickening, nipple retraction).
  - Comparison with previous investigations.
  - Final opinion based on BI-RADS categories 0–6.
  - Therapeutic recommendation.
  - Informing the patient and the referring physician.

TABLE 5 | BI-RADS coding of lesions for mammography and ultrasound (MRI BI-RADS differs from this).

0	Incomplete assessment: additional imaging investigation(s), or comparison with previous ones is/are required
1	Negative
2	Benign
3	Probably benign: short-term (6 months) follow-up or biopsy required (probability of malignancy below 2%)—screening cannot be coded directly as 3
4	Suspected malignancy: histological diagnosis (core biopsy) required (probability of malignancy between 2% and 95%)
4a	Low probability of malignancy (2–10%)
4b	Intermediate probability of malignancy (10–50%)
4c	High probability of malignancy (50–95%)
5	Most likely malignant (≥95%): histological diagnosis required
6	Malignancy confirmed by biopsy: appropriate management is required

TABLE 6 | BI-RADS classification of breast structure types.

BI-RADS A	The breast is almost entirely adipose in structure, the sensitivity of mammography is high
BI-RADS B	Scattered glandular areas of fibroglandular structure
BI-RADS C	Heterogeneously dense glandular parenchyma, that may mask minor lesions
BI-RADS D	Markedly dense glandular parenchyma, the sensitivity of mammography is low

TABLE 7 | Breast structure types according to Tabár.

Glandular	T1
Adipose	T2
Fibroadipose	T3
Adenotic	T4
Fibrotic	T5

Interdisciplinary Cooperation

- Sample handling, cooperation between radiology and pathology.

Aspiration cytology sampling should be performed using a syringe with a rubber stopper. The radiologist performing the sampling should consult the evaluating cytopathologist about the method of smear preparation and fixation, considering that the type of staining used for smear evaluation determines method of fixation, and inadequate smearing may lead to a non-evaluable sample.

- The test order attached to biopsy specimens (preferably a complex radiology report) should include the radiologist's opinion, as well as relevant clinical data available to the radiologist (e.g., any other tumour disease the patient may have).
- Summary report and breast/oncology team opinion:

After each biopsy, regardless of whether the radiological/pathological/clinical opinions are consistent or contradictory, a written diagnostic "Summary Report" must be prepared. This will be issued by the radiologist performing the biopsy and summarizing tests (after consulting with the pathologist, in questionable cases). The purpose of the diagnostic "Summary Report" is to synthesize the results of different (radiological and pathological) diagnostic methods to facilitate further action and/or a therapeutic decision. Based on the results of the assessment, the breast oncology team gives a therapeutic recommendation, possibly proposing complementary tests; all these are recorded in writing in the "Opinion of the Breast Oncology Team".

INVESTIGATION METHODS FOR STAGING AND MONITORING OF BREAST CARCINOMA (OTHER THAN BREAST TESTS)

Methods for Investigating Regional Lymph Nodes

- Ultrasound scanning (35, 65, 66).
- Radionuclide lymphoscintigraphy (radionuclide localization of sentinel lymph nodes) (CT, MRI, PET/CT).

Methods for Investigating Location of Distant Metastases

- Chest, lungs: chest X-ray, CT.
- Mediastinum: CT, MRI, PET/CT (whole body information).
- Chest wall: CT + US, MRI.
- Abdomen: US CT, MRI, PET/CT (whole body information).
- Bone: scintigraphy, 18F-NaF PET (-based measurements) (not yet funded in Hungary), conventional X-ray, MRI, CT, 18F-FDG PET/CT (whole body information) (35, 38).
- Central nervous system:
  - brain: MRI, CT.
  - spinal cord: MRI.
- Lymph nodes (non-regional): US, CT, MRI, 18F-FDGPET/CT (whole body information).

METHODS FOR ASSESSING AND MONITORING THE PRE- AND POST-TREATMENT STAGE

The stage of the disease is determined based on tumour size and certain specific features, regional lymph node involvement, and

the absence or presence of distant metastases (35, 36, 38, 123–125).

For *In Situ* (Stage 0) and Early Invasive (Stage I, II) Breast Cancers

Staging

Of the regional lymph nodes, assessment of the axilla is a mandatory part of the ultrasound scanning of breasts, complemented by guided sampling in the event of any suspicion. No other imaging tests for staging are required if the case is detected by screening, is stage T1N0, has a favourable histology result.

(Note: baseline imaging studies may only have the benefit of providing a basis for comparison for subsequent radiological examinations performed for any reason, such as recording the size and morphology of benign lesions). This may later spare the patient from technically difficult, burdensome biopsies and may make follow-up examinations unnecessary. 18F-FDG PET/CT in the early stages is only recommended for N2–3. At an early stage (I, II, operable III), it may be justified if other investigations or clinical conditions suggest distant metastasis.

For Stage III, IV Breast Cancer and Biologically Aggressive Tumours

Staging

Regions of the neck, chest, abdomen, lesser pelvis:

- CT scan: With MDCT (multi-detector, multislice CT).
- PET/CT is recommended in all cases (stage IIB–IV) when the risk of distant metastases is high; it has been shown to perform better than diagnostic CT staging, and for cases with uncertain or inconsistent results obtained using other procedures. Inspiratory chest CT should also be performed during the PET/CT scanning, if not already performed. If the result of PET is not conclusive for clarifying liver lesions, liver MRI is warranted. If FDG-negative sclerotic bone lesions suggestive of metastases are visualized on PET/CT, bone scintigraphy with SPECT/CT measurements is required. Bone scintigraphy can be replaced by 18F-NaF PET/CT (currently not funded in Hungary).

Follow-Up of Treated Breast Cancer Patients

- Mammography + ultrasound scanning of the treated breast every year for 5 years (unless otherwise specified by the oncology protocol relevant for the patient). After that, annual mammography is recommended.
- Similar actions are required after reconstructive breast surgery, if no implant was used for reconstruction.
- For a breast reconstructed with an implant, modified mammography (Eklund views) + ultrasound should be performed. By default, MRI is not required for implanted breasts for either screening or diagnostic purposes.
- A complex assessment of the contralateral breast is performed annually.
- Even after mastectomy, mammography can almost always be performed on the remaining tissue.
- Breast MRI is indicated after prior consultation with a radiologist:
  - in highrisk cases (young patient, dense breast structure, genetic, familial risk).
  - if recurrence cannot be confirmed by conventional radiological imaging, though it is suspected based on the clinical picture.
  - in other difficult and contradictory cases.
  - due to limited evaluability, MRI is generally not recommended for 6 months after surgery and within 12–18 months after radiation therapy, except for special cases.
- Other imaging tests (e.g., PET/CT) are recommended only if a clinical suspicion arises, being complemented with image-guided sampling, if needed.
- In case of confirmed recurrence, core biopsy is definitely recommended for the assessment of histological parameters.
- Adequate laboratory and imaging tests are recommended to monitor the side-effects of therapy, according to the protocol.
- PET/MRI is currently only available in clinical trials and is currently not funded.

Monitoring of Therapeutic Response Using Radiological Examinations

If there is known dissemination, the oncologist or the treatment protocol will determine the time of follow-up. The choice of imaging method is a joint decision of the attending physician and the radiologist, taking into account the possibility of visualization, availability, and reimbursement (9, 126, 127).

Nuclear Medicine Investigation Methods for Staging

Bone scintigraphy: a nuclear medicine method based on a radionuclide technique. Planar whole-body scanning is considered to be the standard procedure. Currently, bone scintigraphy may be complemented by single-photon emission tomography (SPECT) or hybrid SPECT/CT measurements, in order to increase diagnostic accuracy (37, 94).

^{99m}Tc phosphonate analogues used for scintigraphy show good bone binding and are rapidly washed out from soft tissues. The sensitivity of the test is 90–100% and specificity is around 50–60%. Increased radiopharmaceutical accumulation can be seen in abnormal, metastatic areas due to increased osteoblast activity and enhanced blood perfusion. Bone scintigraphy usually shows lesions significantly earlier than conventional radiological methods. Due to the method's relatively low specificity, 18F-NaF PET/CT (bone PET) is increasingly used in countries that are well-equipped with PET systems (35).

PET and SPECT (hybrid forms of PET/CT and SPECT/CT): The essence of these nuclear medicine techniques is that they map the temporal and spatial distribution of selected pharmaceuticals, molecules, drugs, etc. (biomarkers,

radiopharmaceuticals, radioligands, tracers, etc.) labelled with PET or SPECT isotopes. Photons emitted from the patient are detected in three dimensions (3D) and quantified, or measured semi-quantitatively. Therefore, in addition to the technical development of these systems, use of various tracers and biomarkers is one of their theoretically unlimited strengths. Incorporation of PET and SPECT cameras and radiological imaging equipment (CT, MRI) into a single machine (PET/CT, PET/MRI, SPECT/CT) has significantly decreased examination time (whole body imaging takes 6–10 min) and amount of radioactivity, as well as enabling simultaneous data collection, accurate measurement and localization of quantitative data of functional molecular maps. As a result, diagnostic accuracy and reliability have significantly improved. As well as increasing the high sensitivity, specificity, and positive and negative predictive value (PPV and NPV) of PET and SPECT tests, the use of hybrid techniques also proved to save time and money and allowed the use of significantly lower activities.

Whole-body-18F-FDG PET/CT: provides whole-body information in a single session at a lower radiation exposure than standard contrast-enhanced CT scan(s), identifies distant metastases with the highest sensitivity, and may help to detect possible second primary tumour(s). During evaluation of post-therapeutic lesions and identification of recurrences, as well as being a highly sensitive method, the extent of the disease and possible progression can be visualized using a lower radiation exposure and in a time-saving manner.

18F-NaF-PET/CT: also called "bone PET" may be chosen as an alternative to bone scintigraphy (29–35). In M-staging, a combined use of 18F-FDG and 18F-NaF tracers provides the highest sensitivity, specificity and diagnostic accuracy.

PET/Magnetic Resonance Imaging (PET/MRI): currently this is primarily used in research (37, 40, 41).

Use of Whole-Body Bone Scintigraphy, Complemented With SPECT/(CT), If Needed

Whole-body bone scintigraphy is recommended at an early stage, where the clinical risk of bone metastasis is high at the time of diagnosis and in patients with stage III or IV breast cancer at the time of diagnosis, even in asymptomatic and complaint-free patients (31, 32). Examination is also justified if there is clinical, laboratory or radiological suspicion of bone metastases, during follow-up and long-term care of patients.

For lesions that are unequivocal on bone scintigraphy, it is recommended to complement the scintigraphy with a SPECT, preferably SPECT/CT test to improve diagnostic reliability of bone scintigraphy. SPECT/CT is also recommended for solitary metastases, e.g. when vertebral metastases are suspected, in order to differentiate degenerative and metastatic processes.

Use of 18F-FDG PET/CT

This method is an important step in staging and re-staging assessments, in the event of suspected recurrence, and in all cases where an issue cannot be judged properly using conventional imaging studies or if clinical and imaging data are contradictory or uncertain. The main indication for PET/CT is the assessment of equivocal or suspicious lesions in cases at high risk for metastasis or of already known metastatic disease (35). In view of the whole-body information provided by 18F-FDG PET/CT, this test may be more beneficial than routinely used conventional staging methods in terms of reduced time, costs, and radiation exposure.

For *in situ* and low-risk early (stage I-II) breast cancers, 18F-FDG PET/CT is not recommended as a routine method since:

- It cannot replace sentinel lymph node biopsy.
- In the detection of small metastatic lesions, below the resolution limit of the equipment (typically <5 mm in diameter), the sensitivity of PET/CT is low.

The use of 18F-FDG PET/CT is recommended for:

- Breast cancers that are early stage (I, II) according to conventional staging, but are at high risk for metastases.
- Stage III and IV patients.
- The assessment of recurrences to evaluate the extent of the process, especially for distant metastases (35, 38).
- Differential diagnosis of brachial plexopathy, differentiation between a viable tumour and necrosis/scar tissue, when this is of crucial importance.
- The evaluation of parasternal or mediastinal lymph node metastases—with adequate FDG avidity (IDC-NST, Ki67 > 20%), when PET/CT performs better than other imaging methods.

The Role of PET/CT in the Detection of Bone Metastases

- Bone scintigraphy is more sensitive for osteoplastic metastases, while 18F-FDG PET/CT is more sensitive for lytic and mixed metastases. The two methods do well to complement each other (29–35, 65, 66, 94).
- For screening of bone metastases, bone scintigraphy continues to be the method of choice, complemented by SPECT or SPECT/CT, if needed.
- If bone scintigraphy is negative or uncertain and if there is a strong clinical suspicion of bone metastasis, 18F-FDG PET/CT scanning is recommended (for the assessment of lytic and mixed metastases).
- If 18F-FDG PET/CT has been performed in a patient for any reason and bone metastases have been confirmed (consistently in PET and CT modalities), bone scintigraphy is not required (35).
- If the patient has had FDG PET/CT and on CT scan a sclerotic lesion suggestive of metastasis has been visualized, which though FDG-negative may be a viable bone metastasis, bone scintigraphy with SPECT or SPECT/CT measurements is recommended to confirm this.
- 18F-NaF PET/CT is a method used as an alternative to bone scintigraphy (a procedure that is not yet reimbursed in

Hungary). Also known as "bone PET", it detects skeletal changes with the highest sensitivity (35).

REPORT TEMPLATES AND COMMUNICATION

- Standard report coding and the use of common templates make written reporting (which represents a significant part of radiology work) more accurate and easier, facilitating a closer relationship between radiologist and clinician, effective communication between disciplines and the development of a common language. For development of a common reporting nomenclature, the introduction and consistent use of BI-RADS atlas terms in breast testing is extremely important (23, 128, 129). However, the development of a specific report format is the prerogative of each institution. The standard basic report templates are, on the one hand, recommendations for the format of negative reports (mammography, ultrasound, breast MRI), and, on the other hand, special morphological descriptions of certain pathological lesions. Based on templates, selecting the appropriate option, custom reports may be created, including any specific content when needed.
- The first step in the timely detection of cancers is to provide accurate and comprehensible information to patients about the radiological examinations that are recommended according to patient age, device availability and indications. In addition, efforts should also be made to familiarize patients as much as possible with the predisposing factors for breast cancer, prevention options and risk factors, and the importance of breast density should also be emphasized. Fortunately, there are increasing numbers of more effective campaigns, and more non-profit organizations are undertaking awareness-raising activities. The internet and various social media platforms are also good opportunities for providing information.
- In everyday practice, in addition to the importance of detailed information prior to examinations (informed consent forms), the focus should also be on proper (in-person) communication of investigation results (histological reports, plans for further action, etc.). Trust and collaboration are not only cornerstones of effective doctor-patient communication, but in some cases are also the cornerstones of healing. Breast diagnostics is an area of radiology in which this is of crucial importance.
- With the introduction of the EESZT (Electronic Health Service Space), patients also have access to interim results from pending assessments. This may lead to misunderstandings of diagnoses, inappropriate, self-initiated modification of patient pathways, and overload of the health care system.

In situations where a decision (e.g., therapy or ending the assessment process) is made based on a common end result of related reports, it is appropriate to make a definite reference to this at the end of each report. For example: "We will offer a "summary opinion" based on the pathology report of the targeted sampling performed today together with the radiology report. We ask the patient's attending physician to wait for the 'summary report' when deciding on the therapy, since its content will not necessarily be the same as the content of the two separate reports!".

COMPETENCES, LEGAL AND VERIFICATION ISSUES

Professional Staff

- According to the professional recommendations of the Breast Diagnostic Section of the Hungarian Society of Radiologists, breast imaging tests and image-guided breast interventions may only be performed by a radiologist who has passed the "Complex Radiological Breast Diagnostics" licensure exam (130), with the required minimum technical conditions.
- According to the current requirements of the Minimum Conditions Act (131): at least one licensed specialist must work in a workplace.
- MRI scanning of the breast is also subject to the provisions of licensure exams for breast diagnostics, so breast MRI reports must be produced by a radiologist with such a qualification (or jointly with a licensed radiologist).
- Mammography may be performed by a medical technician with a specific qualification (X-ray technician, radiographer, diagnostic and interventional imaging technician, diagnostic imaging technician).
- The competences of a sonographer do not include the evaluation of breast ultrasound at any age or indication.
- Nuclear medicine investigations: nuclear medicine specialist, specially trained technician.
- Reports of hybrid examinations (PET/CT or PET/MRI) should be compiled jointly by a nuclear medicine specialist and radiology specialist with appropriate experience.

Issues Regarding Forensic Experts

Disputed Radiological Services

In the event of a dispute (e.g., an action for damages), it is up to an expert with proven experience in mammography screening and diagnostics to consider whether the service was provided based on the principle of utmost care. The opinion of a non-radiologist, a general radiology specialist, or a radiologist working occasionally in a low-throughput mammography workplace may not be accepted as an expert opinion. Only the opinion of a radiologist who has passed a complex radiological breast diagnostic licensure test and who has proven to be highly experienced in the given area (e.g., screening, breast MRI) may be decisive.

In order to give an opinion, the expert should simulate a real-life situation; they should not analyse the appropriateness of preoperative diagnosis and therapeutic decision retrospectively, with the benefit of detailed results of all investigations and surgical and histological reports, but it is recommended that they form an opinion only on the basis of the information that was available at the time of the decision(s) contested in the lawsuit.

Disputed Complex Care

Since decision-making about breast diagnostics and therapy requires the synthesis of many aspects (according to the protocol, it is a multidisciplinary (team) activity), it is recommended that forensic expert opinion be reached in a similar way, by a team with appropriate experience, as is the practice in some developed countries. It is not acceptable for a complex process to be evaluated by the representative of only one of the disciplines.

Penalties

- Since the inadequate performance of screening or diagnostic units may jeopardize the lives of many women, greater emphasis should be placed on licensing, quality assurance, and regular supervision of licensees.
- Regular inspections of workplaces performing breast screening and diagnostics are essential, looking at operating conditions, minimum professional (personal and material) conditions and radiation protection.
- The content of the contract signed when opening a screening centre should be verified, and if any errors are revealed, the screening centre may be excluded or replaced with other suitable centres.
- In the event of improper functioning, it is recommended for both screening and diagnostic centres that a warning and an appropriate deadline for correction be given, and that if this deadline is not met, the licence of the centre should be revoked. In the event of a serious fault or deficiency, operation must be discontinued immediately.

Interval Cancers

Mammography screening is an effective but not perfect method: among the group of people receiving a negative result, development of some new cases of cancer in the subsequent screening interval is inevitable. However, the incidence of interval cancers should be kept to a minimum, and their number should be recorded centrally and closely monitored (132).

The history of interval cancers should be systematically traced (in a well-functioning, accessible, searchable national registry).

RECOMMENDATIONS FOR FURTHER DEVELOPMENT OF HUNGARIAN BREAST CANCER SCREENING AND DIAGNOSTICS

Screening of high-risk women (133): Within and in parallel with public health screening, high-risk groups should be identified and separated, and these groups should be screened according to a separate protocol, their data should be collected separately, and separate information materials should be compiled for them. This necessarily requires the expansion of breast MRI and MRI-guided sampling capacity and extensive training of professionals, as well as the collaboration and training of geneticists.

Screening for the 40–44 age group: The known lower performance of mammography for young people is explained by lower parenchyma density, and, due to a lower incidence of breast cancer, decrease in mortality is also lower. At this age, however, tumours may be significantly more aggressive (50).

Recommendation: the professional and financial implications of screening in the 40–44 age group should be examined, and the screening age should be extended accordingly.

Screening of older women: It is recommended that screening be continued over the age of 65 if there is no other serious illness that worsens life expectancy (expected to result in death within 3–5 years). Carcinomas in women aged 65 years or over account for 45% of all new breast cancers, and 45% of deaths from breast cancer also occur in this age group.

Recommendation: professional and financial implications of screening in the 66–75 age group should be examined, and the upper age limit for screening should be extended, in accordance with European practice. When the upper age limit for organized screening is reached, it is recommended that everyone is automatically sent an information letter with an offer to continue screening individually.

Partial increase of screening frequency: According to several international resolutions proposed over recent years, the recommended screening interval for all ages is 1 year. This is due to a lower sojourn time at a younger age, resulting in a significantly higher rate of interval cancers. We also refer here to the practice of Sweden (18 months between age 40–45 and 24 months between age 45–75) and of the United States (12 months), which have the longest screening experience. As the incidence of interval cancer is higher, especially at a younger age, introduction of a screening interval of 18 months is recommended, especially in the of 40–54 age group (50, 132).

Recommendation: examine the professional and financial implications of more frequent screening in this age group and introduce it accordingly.

Digital mammography: In Hungary, the analogue-to-digital switchover has taken place for the majority of mammography devices, at all official screening stations, and this needs to be completed. Since the primary goal of breast screening is to reduce mortality due to breast cancer, this goal can be achieved when the tumour is diagnosed in its initial stage or in a precancer state, which requires optimal technical conditions. Analogue (X-ray film) technology has been excluded from breast diagnostics worldwide and has been replaced by direct digital technology, since direct digital technology has a significantly higher sensitivity for the detection of early breast cancer and DCIS than analogue X-ray film technology. According to the literature, the direct digital technique has revealed twice the number of DCISs, including 8% more high-grade DCISs, than conventional X-ray film mammography (134). For dense breasts, difference between the sensitivity of these two techniques is particularly great in favour of digital technology, and this is of importance primarily for pre- and perimenopausal women and for those under the age of 50. Another important aspect is that direct digital technology uses a lower radiation dose for the patient. Other advantages include fast imaging, possibility of post-processing, easier image storage and reproducibility, and the possibility of telemedicine. When direct digital mammography is used, compliance with technical requirements and quality control

are prerequisites for the applicability of the method in breast screening (3, 135–141).

The use of phosphor storage plate digital technology (CR) in breast screening and diagnosis is strongly contraindicated, since its spatial resolution is lower than that of mammography film and direct digital technology, it requires a higher radiation dose, and some microcalcifications (low-density "powder" calcifications) may remain undetected (142).

Tomosynthesis (3D mammography with 2D synthetic software) is not yet a definite recommendation in international screening protocols, but its use is already clearly recommended in screening and diagnostic algorithms for certain cases (e.g., high-risk women). Research is ongoing into use of this method for screening women at normal risk, with promising results. Reducing the number of interval carcinomas is the issue currently being studied, before the method may be introduced more widely. This method may already be used in individual screening, and it is not contraindicated in organized screening. We recommend unconditional support for tomosynthesis and purchasing new mammography units equipped with this option.

Artificial intelligence: it is recommended that this topic be closely monitored. Gradual introduction in screening should be considered if scientific evidence emerges. At present, none of the dual-reading radiologists can in any way be replaced by AI, since the scientific evidence is not yet sufficient.

Stereotaxis and vacuum-assisted biopsy: These methods have been the gold standard in international practice for many years for the diagnosis of lesions (primarily microcalcifications) that can only be seen on mammography (47). Recommendation: We recommend promoting wider use of these methods in Hungary by settling reimbursement, removing the reimbursement constraint (EFI), and allocating much larger capacity, i.e., a higher number of eligible investigation sites.

BI-RADS: A switch to the more widely used BI-RADS radiology coding of the American College of Radiology (ACR) is recommended, since this is more appropriate than the RKU coding currently in use and also more in line with pathological coding. This system has been continuously updated since 1993, and is optimized to support diagnostic and therapeutic strategy, quality assurance, audit, and better data collection (23).

Renewal of radiation protection regulations and inspection procedures to reduce radiation exposure among the population. Development and integration of quality assurance in digital mammography (125, 143).

Limiting the scope of the license exam to persons: It is proposed to amend the Minimum Conditions Act to make the licensing examination mandatory for each radiologist performing breast examinations, individually. According to the present regulation one single person with such a qualification is sufficient in a workplace, which is not safe enough. More inspections are recommended, and authorizations should be revoked if necessary.

Reimbursement: Reimbursement of breast screening and diagnostics has not changed for more than 15 years or it is not reimbursed, despite the spread of advanced techniques (e.g., digital mammography, tomosynthesis, marker clip, 18F-Na-F PET/CT, tomo-guided stereotaxis, etc.). Some procedure codes are completely missing from the list of activities that are publicly funded (by the National Health Insurance Fund of Hungary, NEAK) or are unduly restricted (e.g., individual funding for vacuum biopsy, performance-volume limit for diagnostic/therapeutic care of those recalled from screening, one FNA/core biopsy limit for one appearance, etc.). All the above hinder performance and development, and ultimately the entire modern patient care, and they should be reviewed. It is recommended that the Secretary of State for Health take steps to arrange for adequate funding for screening and diagnostic procedures and to review this automatically at least every 2 years.

Organizational Proposals for Screening

Objective: to update the Hungarian screening model in every direction, to meet European standards and to maximize efficiency (144, 145).

Interdisciplinary National Screening Working Committee: in 2001, the task of the Interdisciplinary Working Committee, set up by the National Chief Medical Officer, was to give an opinion on the reports of screening centres, to participate in the periodic on-site inspection of centres and in inspections prior to licensing. The procedures of the Working Committee need to be renewed, it needs to operate continuously, and it needs to be granted stronger rights. Otherwise, the existence of personal and financial conditions of screening can be assessed only to a limited extent, its effectiveness can only be estimated, without statistical evidence, and the effectiveness of screening may diminish.

We recommend a reasonable adaptation of screening centres (a reduction in numbers, strict quality control), compliance with technical and radiation protection requirements, and support at organization level (regular condition and stability tests, dosimetry).

It is considered necessary to systematically monitorize the collection of statistical data (e.g., registration of prevalence/incidence screening cycles), to assess the effects of screening based on state-of-the-art breast cancer mortality statistics, to ensure follow-up of patients who have been recommended for surgery but who are lost to follow-up (approx. 34%) by possible merger of the EESZT (Electronic Health Service Space) system.

It is considered important to develop a strategy that is effective at increasing participation (reducing the disadvantages of selection bias), maintaining and verifying regular appearance, with the involvement of trained screening statisticians. This is based on rationally designed screening plans (coordinated activity of the screening centre and entity organizing the screening), specification of call lists, monitoring and correction of professional updates and changes.

Rationalization of calls to the same location and time (individual attendance at the same time of the screening

interval ±1 month). Consideration of territorial characteristics, seasons, seasonal occupancy aspects, consultation with the creators of lists.

Arranging door-to-door transport via screening coordinators, using funded services of the local bus company. Expected benefit: more comfortable, cheaper travel, better attendance rate.

For conditions and expected results, see EU breast screening indicators and the earlier Hungarian screening-diagnostic protocol (1, 2, 90, 146–148). These previous materials are only partially up to date, and require constant updating by the Interdisciplinary Working Committee.

BREAST SELF-EXAMINATION IS NOT A SCREENING TEST

There is evidence that self-examination does not reduce mortality, therefore it should not be suggested that by carrying out self-examination women are substantially benefiting their health or acting against breast cancer (IARC 2015, ACS 2015 recommendations). It should be also noted that medical physical examination does not improve mortality rates either. The state-of-the-art message is: "Women of screening age should have regular mammography screening!" (149).

MEDIA COMMUNICATION AND PROTECTION AGAINST ATTACKS ON BREAST SCREENING MAMMOGRAPHY, AND PUBLIC ADVERTISING AND USE OF NON-EVIDENCE-BASED METHODS

Attacks on breast screening mammography, which has a 40-year history and is backed by strong evidence, and public advertising and use of non-evidence-based, pseudo-scientific methods: these endanger women and decrease the trust in the medical profession and in our achievements so far. These new trends, which lack any foundation, irresponsibly offer "more effective" diagnostic (and therapeutic) methods in the place of the methods and tools used in academic medicine for cancer screening, with an overemphasis on the disadvantages of these methods (e.g., radiation exposure, breast compression). Although these so-called "alternative" test methods detect hardly any (or only a very limited number of) possible lesions in the breast, women still opt for them because they promise to be simpler and offer less discomfort. They are not aware that this deception, which is lacking in any scientific basis, may cost them their lives.

We are observing with great concern how these "testing methods", which do not meet the criteria of evidence-based medicine, have not been evaluated in appropriate clinical trials and do not comply with professional rules of medicine or internationally accepted principles, are advertised without any hindrance by their service providers, and even though these providers are not licensed for such activities, the authorities have not taken effective actions against them. The Radiology Section of the National Advisory Board, the Breast Diagnostics Section of the Hungarian Society of Radiologists and the Hungarian Cancer League have already acted against these "diagnostic methods" and against the advertisement of medical diagnostic methods, but so far with no result.

As physicians, it is our moral duty to raise our voices very strongly to protect women. Therefore, we hereby repeatedly and strongly urge the competent ministry to be partners in eradicating this unsustainable situation.

Our recommendations:

- The Secretary of State for Health should: take a stand on the issue and communicate this to professional organizations.
- Enable the public to be informed about the serious dangers of these activities in the public service media through awareness-raising public service advertisements, similar to traffic safety ads.
- Employ a press and advertising professional to develop a strategy, working with physicians, to eradicate once and for all this phenomenon which threatens women's lives.
- Submit a bill to parliament making it illegal to conduct or promote pseudo-scientific medical activities.

This is part 2 of a series of 6 publications on the 1st Central-Eastern European Professional Consensus Statements on Breast Cancer covering imaging diagnosis and screening (present paper), pathological diagnosis (150), surgical treatment (151), systemic treatment (152), radiotherapy (153) of the disease and related follow-up, rehabilitation and psycho-oncological issues (154).

AUTHOR'S NOTE

The consensus document contains product placement without the intention of advertising. Each complex molecular test is unique, and although these can be described without indicating their name (for example with the number of genes tested), not everyone will necessarily understand what this refers to. For this reason, and adopting the practice used in some of the source works, the tests are listed under their trade name.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.por-journal.com/articles/10.3389/pore.2022.1610382/full#supplementary-material

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Pathological Diagnosis, Work-Up and Reporting of Breast Cancer 1st Central-Eastern European Professional Consensus Statement on Breast Cancer

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This text is based on the recommendations accepted by the 4th Hungarian Consensus Conference on Breast Cancer, modified on the basis of the international consultation and conference within the frames of the Central-Eastern European Academy of Oncology. The recommendations cover non-operative, intraoperative and postoperative diagnostics, determination of prognostic and predictive markers and the content of cytology and histology reports. Furthermore, they address some specific issues such as the current status of multigene molecular markers, the role of pathologists in clinical trials and prerequisites for their involvement, and some remarks about the future.

Keywords: pathology, breast cancer, diagnostics, consensus conference, recommendations

INTRODUCTION

The pathology panel of the 1st Central–Eastern European Professional Consensus Statement on Breast Cancer has based its recommendations principally on the consensus document on breast cancer diagnosis, work-up and reporting achieved at the recent 4th Hungarian Breast Cancer Consensus Conference, which itself was based on previously published national and international recommendations (1–14), of which the newest ones are dealt with in subsequent parts of this document. The original source text took into account the legitimate demands of allied disciplines and the possibilities of pathologists, and changes were made to the text, where deemed necessary as a result of developments since the acceptance of the source document or consultations of the international panel of the Eastern European Professional Consensus Statement on Breast Cancer. The recommendations formulated in this document provide a possible diagnostic,

processing and reporting guideline that may help in the optimal detection and management of breast diseases. The professional panel considers that its guidance should be followed, provided that personal and material conditions are met. The evidence behind these recommendations, apart from those specifically indicated, is mostly of the lowest level and reflect expert consensus, as this is a diagnostic area that has generally not (or only to a limited extent) been validated by clinical trials.

In the diagnosis of breast diseases, non-operative/preoperative diagnostics have become a key starting point for the treatment of patients. Diagnosis obtained intraoperatively has lost its previous significance; it is now accepted that diagnostic steps should be undertaken in all cases to establish the diagnosis before surgery/treatment.

TABLE 1 | Recommended minimum values for selected quality characteristics, based on European directives (6).

Cytology	Minimum	Recommended
Positive predictive value (PPV)	>98%	>99%
False negative rate (FNR)	<6%	<4%
False positive rate (FPR)	<1%	<0.5%
Inadequate rate (INAD)	<25%	<15
Inadequate rate for cancers	<10%	<5%
Suspicious rate	<20%	<15%
Core biopsy		
Positive predictive value (PPV)	>99%	>99.5%
False negative rate (FNR)	<0.5%	<0.1%
(B1+B2) ratio for cancers	<15%	<10%
Suspicious rate	<10%	<5%

NON-OPERATIVE DIAGNOSTICS (PREOPERATIVE OR PRETREATMENT BIOPSY DIAGNOSIS)

Non-operative/preoperative pathological diagnostics is part of the "diagnostic triad" (clinical examination, radiology, pathology). It is important for the pathologist to know the results of other investigations, and to take these into account when giving an opinion on the case. If the pathological diagnosis is made in an isolated setting, without knowledge of clinical and radiological context, this can be a source of serious mistakes and errors. As a minimum requirement for pathological specimens, the localization of the lesion, findings from the physical examination, radiomorphology of the lesion, the radiologist's opinion on the lesion, the method of sampling, and the relevant data in the medical history (e.g., history of malignancy of other organs, pregnancy/lactation at the time of sampling) should be included in the request form. In an optimal situation, the pathological findings, together with the results of other investigations, are placed in an appropriate diagnostic/therapeutic context within a multidisciplinary framework. If all findings are consistent, an appropriate therapeutic decision can be taken, while in the event of inconsistency, further diagnostic steps should be implemented.

It should be noted that, like all diagnostic tests, non-operative diagnostics have limitations. These limitations are reflected by the proportions of "acceptable" false negatives, false positives, non-evaluable and "suspicious" cases specified in the European Guidelines (**Table 1**) (6).

Pathological (cytological or histological) evaluation of a radiologically or clinically detected lesion raising the slightest suspicion of malignancy is always justified for clarification of the lesion; exceptions to this are very rare. For lesions considered benign, confirmation of benignity may also be a goal. Non-operative diagnosis may be established using a sample obtained by guided fine-needle aspiration or core needle biopsy with an automated gun or possibly with a vacuum-assisted biopsy device. For fine-needle aspiration, we recommend the use of European (UK) terminology (6, 13) or the more recent Yokohama terminology (15–17). In essence, the latter does not differ from the earlier European diagnostic category recommendations; rather, these are supplemented with a percentage risk of malignancy (ROM) associated with each category. It is also recommended to supplement the diagnostic categories with the C1–C5 categories, which are easier to use for statistical purposes (e.g., to calculate absolute and complete specificity, or sensitivity of biopsy samples) and which are still not recommended to be used alone.

For core needle biopsies, the B1–B5 category classification is a requirement (**Table 2**) (6, 13, 15, 17), but these categories also cannot stand alone without a written opinion. Efforts should also be made to provide additional information, such as diagnosis, limited prognostic information, histological type for cancers, nuclear or estimated histological grade, prognostic and predictive factors for planned neoadjuvant/primary systemic therapy (PST); see below.

The use of (mainly ultrasound-) guided sampling is recommended even for palpable lessions, due to the possible differences between the palpated and the actual size of the lump or possible necrosis. With the use of image-guidance, it is also easier to establish that there is no other circumscribed lesion responsible for the palpatory finding (e.g., fat lobule), or that the palpatory finding does not match the lesion found on diagnostic imaging.

Calcifications that are suspicious for malignancy should be evaluated primarily using core needle biopsy or vacuum-assisted core biopsy. If, for some reason, such calcifications are still sampled by fine-needle aspiration, a negative result is not sufficient to rule out malignancy; the result of aspiration cytology is only acceptable if it confirms the suspicion of malignancy. Core biopsies have also become relevant in other clinical situations and should be preferred to cytology sampling; if a biomarker assay is likely to be performed when considering or planning PST, it can be performed more reliably on core needle biopsy samples than on cytological specimens (18).

Since atypical ductal epithelial proliferations and DCIS (ductal carcinoma *in situ*) may form a spatial spectrum of lesions, a core needle biopsy taken from the area of microcalcification will not necessarily be representative. The situation may be similar for B3 category papillary and sclerosing lesions. Therefore, excision may be required for a reliable diagnosis of these lesions. A multidisciplinary approach to B3 entities has also resulted in an

TABLE 2 | Definition of non-operative diagnostic categories.

Cytological diagnostic categories	
United Kingdom/European Recommendation (6,13)	Recommendation of the International Academy of Cytology, Yokohama (15–17) (Risk of malignancy: ROM%)
C1: Inadequate (quantitatively and/or qualitatively)	Inadequate (2.4–4.58%)
C2: Benign lesion	Benign (1.2–2.3%)
C3: Atypical, probably benign	Atypical (probably benign) (13–15.7%)
C4: Suspicious of malignancy	Suspicious (of malignancy) (87.6–97.1%)
C5: Malignant (both *in situ* and invasive)	Malignant (99–100%)

Core biopsy categories (6)

B1: Normal breast tissue/Uninterpretable
B2: Benign lesion
B3: A lesion with uncertain malignant potential (malignancy may be associated with ≤25% of cases in the group as a whole).
The followings are typically included in this category
– Some sclerosing lesions: radial scars, complex sclerosing lesions, sclerosing papillomas
– Non-malignant papillary lesions that have not been completely removed
– Lobular (intraepithelial) neoplasia (atypical lobular hyperplasia, classical LCIS; cf. B5a)
– Atypical epithelial proliferation of ductal type (this name is recommended for atypical epithelial proliferation of ductal type found in core biopsies, as quantitative criteria for atypical ductal hyperplasia (ADH) cannot be evaluated in core biopsy samples, so the diagnosis of ADH is not possible on core biopsy)
– Mucocele-like lesions
– Cellular fibroepithelial lesions
– Spindle cell lesions for which other classification is not possible based on the sample
B4: Suspicious of malignancy
B5: Malignant
B5a: *in situ* carcinoma (ductal carcinoma *in situ*, pleomorphic and florid lobular carcinoma *in situ*; compare with B3; note: the United Kingdom recommendation for florid lobular carcinoma *in situ* is B4)
B5b: invasive breast carcinoma
B5c: indeterminate, either an *in situ* or an invasive carcinoma
B5d: other malignant process

Categories C2, B2 (benign) and C5, B5 (malignant) can be considered definitive diagnoses, but these should be interpreted only in a multidisciplinary environment together with imaging and clinical findings, in a "triple diagnostic system". Diagnostic categories should not be used without a written opinion. Categories are primarily useful for statistical evaluation purposes and assist in patient management.

international consensus agreement to avoid over-treatment and under-diagnosis. In a more recent recommendation, among lesions classified B3, diagnostic excision may be avoided in papillary and radial sclerosing lesions. If a vacuum-assisted biopsy is performed and the sample is large enough, a papillary lesion may also be considered a papilloma (B2), and this type of biopsy is sometimes suitable for removing the entire lesion visualized radiologically, and subsequent surgery will not be necessary (19). Establishing and documenting radiopathological correlation and team-based decision-making is mandatory for B3 lesions, especially for vacuum-assisted excisions.

When planning a primary systemic (neoadjuvant) treatment, high-quality core needle biopsy material from the primary tumour should be preferred (exceptionally, incisional biopsy may be acceptable), and in each case, predictive factors should also be determined (as a minimum, oestrogen and progesterone receptor and HER2 status should be assessed, and, if requested, a marker to characterize proliferation, usually the Ki67 labelling index and the proportion of stromal tumour infiltrating lymphocytes (sTIL): see below for details). According to international (European Society for Medical Oncology) recommendations, a core biopsy with several (at least 2–3) tumour tissue cylinders is the expectation in such cases (20). When assessing the effects of therapy, a comparison of the histological picture of the tumour in the core needle biopsy and after neoadjuvant treatment is also an internationally recommended requirement (12).

It is a generally accepted view that mastectomy cannot be performed based solely on cytological opinion, but this may be acceptable in exceptional cases involving reliable, well-synchronized teams. If the cytological and radiological opinions differ markedly, (e.g., C2/R4-5 or U 4/5 or C4-5/R1-2 and U1-2), repeated sampling and core needle biopsy should always be considered.

Efforts should be made to evaluate both histological and cytological specimens in reliable, quality-assured laboratories. Departments are expected to participate in external quality control programmes and meet compliance requirements. Pathology reporting of breast samples also requires sufficient skills, for which there are no defined criteria in most countries, but an international recommendation (EUSOMA: European Society of Breast Cancer Specialists) sets the minimum workload required for proficiency at 50 cases of early breast cancer surgical specimens, prefereably 100 (but at least 50) non-operative/preoperative samples and 25 metastatic cases per year (21). Secondary certification exams (e.g., cytology) might also be a requirement for recognizing proficiency in countries where such graduation exists.

Non-operative diagnosis of lymph node status will be discussed in the section on lymph nodes.

Processing Core Biopsies

It is essential that the tissue cylinders are placed into the block parallel to their longitudinal axis. Usually 2–3 cylinders, 1 mm in

thickness and 10 mm in length are obtained for assessment. [The number of cores (tissue cylinders) will determine how representative the biopsy is and is proportional with the likelihood of establishing a correct diagnosis (22)]. These are examined by following the rules for small biopsies and if needed, multiple layers are obtained. It may be advisable to place serial tissue sections immediately on pretreated slides since the area in question may be cut out before immunohistochemistry is performed. Haematoxylin-eosin (HE) stained sections placed on treated slides are also suitable for performing immunohistochemical reactions in a second step. For a core biopsy (or other small-volume biopsies), it may be necessary to prepare a relatively large number of sections in several rounds, which leads to significant material loss due to multiple trimmings and sectionings. In such cases, the sample should be further examined after dividing it into multiple parts (e.g., if tissue cores were embedded into a single block, they should be reembedded into separate cassettes, or longer cores should be halved). This may be needed since PST may result in complete or nearly complete regression, and when a new tissue-based predictive test is required in such cases, the remaining core biopsy of the primary tumour may be the most readily available sample. Providing a core biopsy tumour sample may also be an inclusion criterion for participation in clinical trials. Quantitative characterization of the relevant lesion present in the core biopsy is also recommended [for example, in addition to the nature of the pathological abnormality responsible for microcalcification—e.g., columnar changes, flat epithelial atypia (FEA), atypical epithelial hyperplasia—the percentage or length in mm can be given].

From core biopsy samples obtained before neoadjuvant treatment, tumour characteristics influencing the treatment should be determined, and in addition to predictive factors, the following should also be described, if possible: vascular invasion and presence of an *in situ* component; more recently, neoadjuvant treatment may require quantification of stromal tumour infiltrating lymphocytes (sTILs) (23).

Another diagnostic modality of biopsy is vacuum-assisted biopsy (VAB; vacuum mammotomy), which is performed with a 7G to 11G needle under ultrasound (US), stereotaxis or magnetic resonance imaging (MRI) guidance. It is a minimally invasive breast biopsy that removes more tissue than traditional gun CNBs, allowing the removal of smaller lesions, making VAB a therapeutic alternative for some lesions (19). For vacuum-assisted biopsies, larger volume samples are processed, in the form of tissue cylinders or smaller fragments, depending on the device. If cylinders containing calcification have been separated by the sampler, it is advisable to process them separately during histological examination. If necessary, decalcification using EDTA (ethylenediamine tetraacetic acid) is recommended; the use of strong acids should be avoided (24).

For tissue biopsies taken from microcalcifications, it is advisable to indicate the approximate size of calcifications on microscopic examination since small calcifications (below 50 μm) are unlikely to be detected on mammography, unless multiple similar foci are superimposed; thus, stating the size of calcifications helps to establish a proper radiopathological correlation. If the core biopsy/vacuum-assisted core biopsy was performed because of microcalcification, specimen radiography of the sample is a requirement (this will validate sampling) and, optimally, calcified particles may also be sent separately for analysis. If microcalcificates do not appear in the first sections, deeper sections will be required. If microcalcifications cannot be confirmed by routine microscopic evaluation, polarized light may be helpful, since calcium oxalate crystals (weddellite) are refractile and polarizable but usually clear or tinged yellow in H&E sections (25).

Exceptionally (e.g., after multiple unsuccessful cytological or core biopsy samplings of a large, radiologically suspicious lesion; for extensively ulcerated, advanced breast tumours; in Paget's disease; for very superficial lesions), a minimally invasive surgical intervention may also serve as a preoperative diagnostic method (incisional biopsy).

INTRAOPERATIVE EXAMINATIONS

- Intraoperative examinations may be macroscopic examinations with the naked eye or microscopic examinations (analysis of imprint or scrape cytology samples or frozen sections). All of these have limitations compared to permanent section histology; it should be highlighted that the quality and evaluability of frozen sections is poorer than that of permanent sections. Intraoperative molecular tests are not performed in most central—eastern European countries. There are also examples of intraoperative immunohistochemistry in the literature, with both imprint cytology and frozen section variants increasing the sensitivity of lymph node examination; however, these generally reveal only small metastases that would not affect the outcome of surgery, therefore routine intraoperative immunohistochemistry is not justified.
- For large lesions found to be *in situ* carcinomas on radiological and/or preoperative pathology examinations, and for lesions detected exclusively in the form of microcalcifications, intraoperative frozen section examination is meaningless because it does not help to clarify the diagnosis and may render the tissues unsuitable for making the eventual diagnosis. For this reason, no frozen section exam is performed on such samples.
- Frozen sections must not be prepared from lesions of 10 mm or less, since failure to obtain a sufficient quantity and quality of tissue from the lesion for embedding will jeopardize definitive diagnosis and also the ability to assess prognostic and predictive factors for small invasive tumours. If there is a definitive preoperative diagnosis, there is no need for intraoperative examination to confirm this diagnosis. Frozen sections should not be used merely to compensate for inadequate preoperative evaluation.
- The indications for frozen section examination have become significantly limited. In exceptional cases, if attempts to obtain a preoperative diagnosis have failed, a

multidisciplinary decision may be made to examine frozen sections; this may also be justified if there are insufficient or uncertain preoperative findings, in similarly very rare instances.
- The aim of intraoperative examination may also be the assessment of surgical resection margins or the distance between the tumour and the tumour-free margin. These examinations can be performed as imprints (cytology), frozen sections and macroscopic measurements. (In the latter cases, the original resection surface must be marked with dye before incision!)
- Intraoperative examinations may also be done to assess sentinel lymph node status.
- The final decision on the nature and feasibility of an intraoperative examination is made by the pathologist.
- Molecular tests, tissue banking: If the infrastructure allowing tissue samples to be frozen and stored at −80°C is available, it is recommended that a part of the tumour tissue be stored in this manner after proper orientation of the freshly resected tissue and marking of surgical surfaces (see below). Of course, tissue banking can be inititated only if this does not reduce the diagnostic possibilities; the priority should be for making the proper diagnosis and for assessing parameters influencing treatment. A key point of whole tissue biobanking is the time factor of the ischemia of the harvested tissue. According to several studies, it is recommended that the material be collected for freezing within 15–30 min after the interruption of the blood supply in order to minimize the hypoxic damage. If the specified time of ischemia is exceeded, irreversible processes could occur at the molecular level, which would impair the quality of biomolecules. As the time interval between surgical resection and freezing of the tissue is relatively short, biobanking requires a perfect interaction and cooperation of the workplaces involved, as well as experienced and trained pathologists.

POSTOPERATIVE DIAGNOSTICS—PROCESSING, PRINCIPLES OF COOPERATION

- Surgical materials should be sent for pathological examination accompanied by clinical data described for non-operative diagnostics. If neoadjuvant treatment has been administered, it is essential to state this, indicating original tumour size, location, tumour data obtained from a biopsy specimen taken prior to treatment, nature of the treatment, and the clinically evaluated response to treatment. The pathologist should be informed of the type of surgery. Surgical resections (breast operations) are divided into breast conserving procedures (inclusive of excision, segmental resection, lumpectomy, quandrantectomy, segmental/sectoral or partial mastectomy . . . etc., with or without axillary surgery and different methods of oncoplastic surgery) and total mastectomy (simple, skin-sparing, nipple-sparing, modified radical and radical mastectomy).
- The surgical specimen should be made available to the pathology department/pathologist immediately after removal (within a maximum of 30–60 min), without fixation and incision. If this is not feasible, the guidelines for sample fixation described under the section on "Special assessment of prognostic and predictive factors" are to be followed. Correct processing generally requires a preoperative mammography and specimen mammography image annotated by the radiologist and the related radiology report to be available to the pathologist at the time of the cut-up. This is essential for most breast-conserving surgeries, multifocal tumours, extensive DCIS, and surgical preparations following primary systemic treatment. It is recommended that macro-photography and/or a simple drawing be done of the slices, especially for small lesions, and that a specimen mammographic image of the slices be captured, especially for lesions with microcalcifications.
- The multifocal character of the lesion is determined primarily by the radiologist and secondarily by the pathologist. Instead of conventional classification of tumours with multiple foci (multifocal or multicentric), it is advisable to mention a certain number of focal lesions or multiple tumours/tumours with multiple foci. pT classification is made based on the largest focus, with indication of multifocality, since this is associated with a worse prognosis (26–28). Besides pT classification, it is also advisable to specify the extent of the tumour, which is the distance between the most distant margins of the two most distant foci, i.e., the largest dimension of the breast parenchyma affected by the tumour. This may play a role in the planning of customized oncological therapy.
- As with all measurements, both macroscopic and microscopic assessment of tumour size is approximate, but it is essential that this be recorded. At a minimum, the greatest dimension of the tumour should be given. (This may fall into a different plane than the plane of slicing, therefore requiring the assessment of tumour size in all three dimensions.) If there is a discrepancy between macroscopic and microscopic measurement, the latter shall prevail, unless the tumour is so large that it is impossible or meaningless to measure it microscopically.
- Regardless of its size, the tumour should be processed in a representative manner, ideally achieved by examining the entirety of the cut surfaces in multiple planes. For large tumours, a minimum of 1 block/1 cm is recommended.
- The surgical specimen should be marked in the operating room, ideally *in situ* (e.g., with surgical stiches) (with at least three clear, ideally radiopaque markers, such as medial, lateral, superior pole; or central/mammillary, peripheral and clockwise; or with insertion of two sutures and specifying the side) for a proper orientation. The fact of orientation should also be recorded by the pathologist. It is recommended that the surgeon marks the fascia (e.g., with 4 clearly identifiable sutures placed at its borders) and that

both the surgeon and pathologist make a statement about its presence. In nipple-sparing surgeries, identification of the retromammillary region is essential, and this should therefore also be labelled by the surgeon. The size of the surgical specimen is specified in cm in three dimensions, and its weight is also given, since this is the simplest and best way to characterise the volume, and can be used as a basis for assessment of certain surgical quality indicators.

- To allow the assessment of the resection margins, staining the resection surfaces of the surgical specimen is essential: most simply with one colour, but with at least two different colours (e.g., black—anterior surface, blue—posterior surface) to facilitate subsequent orientation, and ideally with 6 colours. Our understanding of the recommended minimum tumour-free margin has changed significantly recently. For early invasive breast cancer (stage I and II), on the basis of consensus based on results from randomized trials and meta-analysis (highest level of evidence), a margin is considered positive (i.e., justifying re-excision) when dye is seen on tumour cells (invasive or *in situ* component)—"ink on tumour" (29, 30). On the one hand, it should be emphasized that evidence for this recommendation does not apply to pure *in situ* carcinoma, patients receiving PST or tumours in patients who have undergone accelerated partial breast irradiation (APBI) (31), while on the other hand, we should be aware of the technical limitations which as a consequence may mean that the presence of dye does not necessarily indicate a resection surface (e.g., in case of artificial cracks in the adipose tissue, dye may seep into deeper layers; for tissues removed in multiple fragments, the relationship between them becomes uncertain). We should also be aware that—based on individual considerations—re-excision may be reasonable even in the absence of a tumour-positive margin, when phenomena associated with a higher risk for residual tumour (large tumour volume in the immediate vicinity of the margin, discontinuous growth pattern such as an extensive intraductal component, lobular histological type or diffuse infiltration) are present. For purely *in situ* tumours, a similarly high level of evidence for assessment of positive margins is not available. For DCIS, an international panel recommends a tumour-free margin of 2 mm (29), while for classical lobular neoplasia (LN), a tumour-positive margin does not imply any further therapeutic indication. (Since its introduction by Haagensen, LN is an umbrella term for atypical lobular hyperplasia and *in situ* lobular carcinoma, not including invasive tumours; however, it may be sometimes qualified by additional adjectives: e.g., non-invasive LN—see below under histological types). For pleomorphic and/or florid lobular neoplasia (pLCIS, fLCIS), there is no high-level evidence overriding previous treatment recommendations, which are similar to those relating to DCIS. Retrospective studies have shown that a pLCIS/fLCIS in the resection margin is associated with invasive lobular carcinoma in a sufficiently high proportion of cases to represent an additional treatment indication (31). For margin assessment in the multidisciplinary setting, an important additional information in the description of the surgical operative procedure may be whether the excision toward the chest has reached the fascia (or not). Taking color digital pictures made during the cut-up of the surgical specimen (including both the original specimen and the inked slices) and correlating them with scanned (digitized) histological slides helps to demonstrate the localisation of the positive surgical margins during the multidisciplinary discussion.
- It should be clearly identified whether there are one or more abnormal masses in the parenchyma.
- Blocks are sequentially numbered so that the location of each block within the original preparation can be accurately traced back based on the macroscopic description.
- All areas that appear abnormal, all parenchyma fragments containing microcalcification, are sampled in a sufficiently representative manner. If mammography images or macro photos of the slices have been captured, it is advisable to indicate the location of blocks on the film/digital image or on a schematic drawing. A schematic drawing that also reflects orientation often carries more information than a block list and lengthy descriptions, which may be expressed in local jargon. For this reason, it is important to have this visual information to hand during reporting, and (for example) if an external consultation is requested, a copy of these drawings (block maps) should also be sent to the consulting professional.
- Besides sampling from the tumour for histological examination, it is also essential to sample apparently intact areas around the tumour, including surgical resection surfaces.
- If a marker clip has been inserted, its documentation (its absence or presence on specimen mammography) is part of the pathological assessment.
- The remaining slices of the specimen are to be kept in order and stored in a way that best enables reconstruction (e.g., wrapped in gauze).
- Re-excision is required if excision was not performed with negative margins; the specimen from the re-excision should also be oriented, primarily in order to establish the relationship with the previous excision. This is the only way to perform the pathological evaluation of the new resection surfaces.
- When there is a discrepancy between a clinical diagnosis and the diagnosis of the surgical material, a comparison with a preoperative biopsy specimen may resolve this contradiction; therefore, if preoperative assessment was performed at another institution, it is recommended that the pathological specimen be requested and reexamined.
- If uniform orientation principles are adhered to, there are few cases in which, due to uncertainty, it may be necessary for the surgeon to review the surgical material before slicing, but in such cases, it is inappropriate to omit this step.

Postoperative discussions provide an excellent opportunity for verifying that the screen-detected and removed tumour was identical.

- In the vast majority of cases, intraoperative specimen mammography is performed in the radiology department that previously diagnosed the lesion. Pathology departments may also perform this examination if they are properly equipped, but the captured image should always be compared with the original mammogram. During pathological processing, the presence of the original mammographic image and comparison with specimen mammography are also important. If the pathologist has any issues with the interpretation of the specimen mammogram, consultation between the two professions is warranted. Optimally, a joint evaluation in person should be carried out; this is not always possible, but it can be replaced by various alternative solutions (e.g., consultation *via* remote communications). If an MRI has also been performed, preferably the MRI report and the visual material of the scanning should be made available, along with the possibility of consultation with a radiologist experienced in breast diagnostics (including reporting of breast MRI).
- Preparation of megablocks/large blocks and sections is recommended, as far as possible. For a more widespread use of the method, this recommendation is strong, since larger sections (sections of 4 × 6 cm or 5 × 7 cm are most common) allow for a more accurate radiopathological correlation, and a more accurate assessment of tumour size. These large blocks and slides may be prepared in pathology laboratories containing the usual infrastructure. Significantly larger sections also exist, but a special infrastructure is required in order to make them, prepare them for storage and store them. In the absence of whole slice giant blocks, digital reconstruction following scanning of sections obtained from conventional and/or mega-cassette blocks representing the entire slice may be a bypass solution. The use of large block technique is especially recommended for diffuse processes (diffuse calcification, diffusely infiltrating lobular carcinoma) and for multifocal tumours. Small (conventional) sections can only provide information of similar accuracy to large sections if they are available in large number and with complex orientation reconstruction (32), but this is much more time-consuming. In addition to large sections, it is always advisable to prepare tumour blocks of conventional size, since these allow a simpler and more economical assessment of prognostic and predictive markers by immunohistochemistry.
- With mastectomy, processing of the nipple and areola is recommended.
- For a PST, the area originally containing the tumour (optimally, clearly marked prior to treatment in a way that is visible for the pathologist), as well as its surrounding area, should be processed in detail to determine actual regression. Radiopathological comparison (specimen mammography, specimen mammography of slices) and giant block technique are recommended. Particular attention should also be paid to the detection of multifocality. If necessary, in addition to routine HE staining, cytokeratin immunohistochemistry may be used to detect residual tumour in the event of uncertainty. Comparison with a previous core needle biopsy specimen may help the assessment of regression (12). For quantifying the degree of regression, we suggest the scheme shown in **Table 3** (12). The RCB (residual cancer burden) calculator, developed by the MD Anderson Cancer Center is suitable for quantification of the residual tumour volume. This calculator uses the two largest dimensions of the tumour containing tumour bed, its cellularity, including the percentage of the *in situ* carcinoma component, as well as the number of metastatic lymph nodes and the size of the largest metastasis, as variables (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3) (33). The advantage of this over other methods is that it strives to estimate residual tumour volume based on two dimensions and cell density, and it takes into account not only the primary tumour, but also lymph nodes (34). Pathological complete regression (pCR) can only be stated based on complete (or for large original tumours, a very thorough partial) processing of tumour bed and processing of removed lymph nodes. pCR is achieved when there is no residual invasive carcinoma in the breast and lymph nodes are also completely tumour-free: TR1 and NR1 or NR2 (35). It should be noted that for the measurement of a residual tumour in the tumour bed, the eighth edition of the AJCC Cancer staging manual sets out different principles than the guide for RCB assessment (33, 36). For the former, besides disregarding regression-induced fibrosis, the largest dimension of the largest residual tumour focus in the tumour bed is used as the basis for ypT classification (36); in the latter, the "wall to wall" distance between the most distant tumour foci in the tumour bed, with the omission of marginal fibrosis, will give the largest dimension. In the rare case, when residual tumour is found only in small vascular spaces, no primary tumor size is to be given, an this is recorded as ypT0 L1 (for the presence of lymphovascular invasion); such cases do not qualify for pCR.

TRADITIONAL PROGNOSTIC (PREDICTIVE) FACTORS

Parameters of the Primary Tumour

One of the most important prognostic factors of breast carcinomas is the size of the invasive tumour. This should always be specified based on the largest size of the largest focus, and this is the size that determines the pT category of

TABLE 3 | Suggestions for assessment of the regression of primary tumour (TR) and lymph node metastasis (NR) (12).

Primary tumour (TR)
1: Complete pathological regression
a: no residual carcinoma
b: no residual invasive carcinoma, but residual DCIS is present
2: Partial therapeutic response
a: minimal (<10%) residual (invasive) tumour
b: clear response to therapy but with 10–50% residual (invasive) tumour
c: clear response to therapy but with >50% residual (invasive) tumour
3: No signs of regression
Lymph nodes (NR)
1: No metastases, and no visible signs of regression
2: No metastases, but visible signs of regression
3: Metastasis with signs of regression
4: Metastasis without signs of regression

Lymph nodes showing multiple different therapeutic responses should be classified based on the worse response. (TR stands for primary Tumour Regression/Tumour Response, NR for Nodal Regression/Nodal Response.). (Original (i), (ii) and (iii) subcategory designations (12) have been modified to a, b and c, respectively.)

pTNM (**Table 4**) (12, 36–38). If possible, it should be measured microscopically, but for large tumours, macroscopic measurement is also acceptable. Whole tumour size, including the *in situ* carcinoma component, is important when determining locoregional treatment, so it is essential that this be specified separately. An extensive intraductal component (EIC) is usually defined as a DCIS, which accounts for >25% of the dominant invasive tumour focus and extends beyond its margins to the surrounding breast parenchyma, or as a tumour that is predominantly DCIS but contains invasive foci (39). Since such a definition of invasive tumour size and total tumour size is only obvious for unifocal tumours, tumour extent should also be specified for multifocal tumours, replacing whole tumour size; this is the largest dimension of the breast parenchyma affected by the tumour. For unifocal tumours, extent coincides with the whole tumour size. Invasive tumours may be unifocal, multifocal, and diffuse in appearance. The area between foci of multifocal invasive tumours may include tumour-free breast parenchyma, benign lesions (26, 27), or *in situ* carcinomas (27). Tumours with multiple foci of invasion can manifest in various forms: e.g., invasive carcinoma with satellite foci of invasion (the International Collaboration on Cancer Reporting (ICCR) recommends to include the size of the satellite focus and separating tumour free area in the invasive tumour size if the distance between the satellite and main tumour is less than 5 mm, and not to add the two if the distance is greater than 5 mm), EIC with multiple foci of invasion (the ICCR recommendation being to measure the largest distance between the two most distant invasive foci for invasive tumour size), multiple biologically different invasive carcinomas (considering them as two diseases if separate), cancer with extensive lymphovascular invasion (LVI; where LVI is not added to tumour size, but is part of the extent), or the tumor can be arteficially fragmented (38). Descibed scenarios may often require very individual approaches. A main feature of diffuse invasive cancers is the radiological and pathological absence of a well-defined tumour body and a spider web-like appearance (26, 27). The size of the invasive component of the tumour, whole tumour size, and tumour extent are similarly evaluated after PST, and these parameters should be determined in such cases, as well. It should be mentioned again that the AJCC recommendation for measuring the size of an invasive tumour and of lymph node metastases requires the omission of regression fibrosis when assessing tumour sizes (36), and this differs from the measurement recommended for RCB assessment (33).

In situ carcinomas can be similarly classified according to their pattern and distribution: a lesion is unifocal if it involves one single terminal ductal-lobular unit (TDLUs) or more such units located close to each other within a coherent area. An *in situ* carcinoma is multifocal (multiple) when TDLUs involved are further apart from each other and are not connected. According to Tot's classification, an *in situ* carcinoma is considered diffuse when it primarily involves large ducts. The distribution of invasive and *in situ* carcinoma may also be summed up according to a combined pattern; if any of the components is diffuse, then the whole tumour should be interpreted as a diffuse tumour. If an invasive or *in situ* carcinoma forms multiple foci, it will be a multiple (multifocal) tumour, and it may only be considered a unifocal tumour if its invasive (and/or *in situ*) component is present in the same single focus (25, 26). Besides influencing surgical treatment, this classification also has prognostic value.

Histological type of tumours should be specified according to the WHO (World Health Organization) classification (**Table 5**) (40). The heterogeneous group of tumours formerly called invasive ductal carcinoma remains no special type (NST) breast cancer, suggesting that these cancers do not contain characteristics based on which they could be classified as special type cancers. The group name introduced in the 4th edition of the WHO classification was left unchanged in the 5th edition of the WHO classification (40). The classification has become significantly simpler, with a significant proportion of rare breast tumours previously classified as special tumour types now being identified as morphological variants of NST carcinomas.

For invasive epithelial tumours, differentiation is based on the Nottingham combined histologic grade system (**Table 6**) (6). For invasive tumours, the Nottingham Prognostic Index (NPI) with a proven prognostic value may also be calculated, see **Table 7** (7) for help. Although prognosis of breast cancer has significantly improved since the original description, the NPI still differentiates between various prognostic groups despite better overall survival, though differences between the prognostic groups are smaller; and as an example, prognosis for the "excellent prognostic group" and the "good prognostic group" is essentially not differentiable (7). For tumours classified as pure DCIS, we also propose a three-tiered system for reporting differentiation (**Table 8**) (41). For the assessment of DCIS grade, there are several systems in which nuclear sizes are defined in different ways if defined at all (42); the use of these

TABLE 4 | Definition of cTNM and pTNM categories for stage classification of breast cancers based on the eighth edition of the TNM (2017) (36, 37).

cT (T) and pT — primary tumour	
Pathological T category: same as clinical T classification, but only the largest dimension (rounded to the nearest mm value) of the invasive component measured on histological section will count when stating size. For larger tumours that cannot be measured microscopically in one block, the macroscopic size is also appropriate, according to the eighth edition of the TNM.	
Tx	The primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*.
Tis (DCIS)	Ductal carcinoma *in situ*.
Tis (LCIS)	Lobular carcinoma *in situ*[b]
Tis (Paget)	Paget's disease without associated *in situ* or invasive tumour (if Paget's disease was associated with an *in situ* or invasive breast cancer, the latter is classified according to tumour size)
T1	Invasive tumour of 2 cm or less in size
T1mi	Microinvasion of 0.1 cm or less in size
T1a	Tumour is larger than 0.1 cm, but does not exceed 0.5 cm.
T1b	Tumour is larger than 0.5 cm, but does not exceed 1 cm
T1c	Tumour is larger than 1 cm, but does not exceed 2 cm
T2	Tumour is larger than 2 cm, but does not exceed 5 cm
T3	Tumour is larger than 5 cm
T4	Tumour of any size spreading directly to the chest wall (a) or skin (b)
T4a	Spread to chest wall
T4b	Oedema ("peau d'orange") or ulceration of the skin or satellite skin nodules in the same breast
T4c	If criteria T4a and T4b are present at the same time
T4d	Inflammatory carcinoma (primarily a clinical staging category)
cN—clinical classification of regional lymph nodes (cN and N categories are synonymous)	
cNx	Regional lymph nodes cannot be evaluated. (e.g., have been previously removed.)
cN0	No regional lymph node metastases found
cN1	Metastases in ipsilateral level I or II mobile lymph node(s)
cN2	Metastases in ipsilateral fixed/conglomerate lymph node(s) or clinically detectable[a] metastases in ipsilateral lymph node(s) adjacent to the internal mammary artery, not associated with clinically detectable[a] axillary lymph node metastases
cN2a	Metastases to ipsilateral surrounding structures or to (a) fixed/conglomerate lymph node(s)
cN2b	Clinically detectable[a] metastases in the lymph node(s) adjacent to the internal mammary artery, in the absence of clinically detectable[a] axillary lymph node metastases
cN3	Clinically detectable[a] metastases in ipsilateral infraclavicular (level III axillary) lymph node(s), regardless of the involvement of level I, level II lymph nodes; or clinically detectable[a] metastases in the lymph node(s) adjacent to the internal mammary artery and in axillary lymph node (s); or clinically detectable[a] metastases in supraclavicular lymph node(s), regardless of the involvement of other regional lymph nodes
cN3a	Metastases in infraclavicular lymph node(s)
cN3b	Clinically detectable[a] metastases in ipsilateral lymph nodes along the internal mammary artery together with 1 or more metastatic axillary lymph nodes
cN3c	Ipsilateral supraclavicular lymph node metastases
pN—pathological classification of regional lymph nodes	
At least level I dissection is required for classification and the number of lymph nodes examined should be at least 6. (TNM recommends a minimum of 6 lymph nodes, but this is for lymph node dissections and is not valid for sentinel lymph node biopsy and axillary sampling earlier performed in some United Kingdom and Scandinavian units; if there are more than 6 sentinel lymph nodes removed, the "(sn)" postscript is not applicable)	
pNx	pNx Regional lymph nodes cannot be assessed. (Not removed for examination or have been previously removed.)
pN0	No regional lymph node metastases
pN0(i-)	No histologically detectable regional lymph node metastases, negative IHC
pN0 (i+)	Histologically confirmed lymph node involvement not larger than 0.2 mm or less than 200 tumour cells. (The size of the largest contiguous group of cells, if there are more groups, while in the absence of such groups the number of cells should be the criterion.)
pN0 (mol–)	No regional lymph node metastases histologically, and negative molecular biology findings (usually RT-PCR or OSNA—one step nucleic acid amplification)
pN0 (mol+)	No regional lymph node metastases histologically, and positive molecular biological findings (usually RT-PCR or OSNA)
pN1mi	Micrometastasis (larger than 0.2 mm, but not larger than 2.0 mm)
pN1	Metastases in 1–3 ipsilateral axillary lymph nodes and/or lymph nodes along the internal mammary artery; in the latter case, detected by sentinel lymph node assessment, but clinically not detectable
pN1a	Metastases in 1–3 axillary lymph nodes
pN1b	Metastases in the lymph nodes along the internal mammary artery, microscopic disease detected by sentinel lymph node examination only, not detectable by imaging studies or physical examination

(Continued on following page)

TABLE 4 | (*Continued*) Definition of cTNM and pTNM categories for stage classification of breast cancers based on the eighth edition of the TNM (2017) (36, 37).

cT (T) and pT — primary tumour	
pN1c	Metastases in 1–3 axillary lymph nodes and in lymph nodes along the internal mammary artery, under conditions described at pN1b, for the latter
pN2	Metastases in 4–9 axillary lymph nodes, or internal mammary lymph node metastases detected by physical examination and/or imaging, without axillary lymph node metastasis
pN2a	Metastases in 4–9 axillary lymph nodes
pN2b	Clinically detectable metastases along the internal mammary artery without axillary lymph node metastasis
pN3	Metastases in 10 or more axillary lymph nodes or infraclavicular lymph nodes; or clinically detectable metastases in internal mammary lymph nodes in the presence of 1 or more metastatic axillary lymph nodes; or metastases in more than 3 axillary lymph nodes with clinically non-detectable microscopic metastases along the internal mammary artery, or ipsilateral supraclavicular lymph node metastases
pN3a	Metastases in more than 10 axillary lymph nodes or metastases in infraclavicular lymph nodes
pN3b	Clinically detectable metastases in lymph nodes along ipsilateral internal mammary artery with 1 or more metastatic axillary lymph nodes; or metastases in more than 3 axillary lymph nodes and in the lymph nodes along the internal mammary artery, the latter being detected only on sentinel lymph node examination, but not detectable clinically
pN3c	Ipsilateral supraclavicular lymph node metastases.
"pN1mi(mol+) and pN1(mol+)" Categories not accepted by the eighth edition of TNM but recommended by the European Working Group for Breast Screening Pathology and the International Collaboration for Cancer Reporting for labelling of metastases with a volume greater than pN0 (mol+), which are analysed (and thus identified almost exclusively) using quantitative molecular analysis (12,39).	
M—distant metastases (categories cM and M are the same).	
cM0	No distant metastases
cM1	Evidence of distant metastasis.
Distant metastasis is classified as pM1 only if it has undergone histological or cytological examination (i.e. metastasis has been surgically removed or sampled by biopsy); otherwise the categories are (clinical) M categories (categories Mx, pMx, pM0 are not defined).	

Stage classification			
Stage	T	*N*	M
0	Tis	N0	M0
I A	T1[c]	N0	M0
I B	T0, T1[c]	N1mi	M0
II A	T0, T1[c]	N1	M0
	T2	N0	M0
II B	T2	N1	M0
	T3	N0	M0
III A	T0, T1[c], T2	N2	M0
	T3	N1, N2	M0
III B	T4	N0, N1, N2	M0
III C	any T	N3	M0
IV	any T	any N	M1

[a]*Clinically detectable: structure discovered on clinical examination or imaging (excluding lymphoscintigraphy) that raises a well-founded suspicion of malignancy, or which proves to be metastatic by non-operative biopsy. The basic requirement for pN classification is pT classification after tumour removal. Consequently, if the primary tumour is not removed, only cN classification is possible, even when microscopic examination is performed on an aspiration cytology or core biopsy sample; in such cases, the suffix "(f)" refers to the microscopic examination—e.g. cN1 (f).*

[b]*The wording used in the 8th edition of the AJCC, and UICC, sources related to stages and classifications differs (36, 37). According to the former, LCIS (lobular carcinoma* in situ*) is not classified as pTis, while in the latter it belongs to pTis group.*

[c]*Including T1mi. The stages described above are those included in the TNM classification issued by the UICC, and are identical with the AJCC Cancer Staging Manual defined anatomical stages, but different from prognostic stages described in the latter source, which, in addition to ER, PR, and HER2 statuses, include grade and, when available, the recurrence score based on the Oncotype Dx test. Prognostic stages may deviate from anatomical stages by up to two subcategories in either direction (36). Dynamic changes in these prognostic stages are expected, although the provided Ref. (36) lists them on several pages, the use of online calculators could be simpler, when needed (e.g., https://reference.medscape.com/calculator/594/breast-cancer-pathological-tnm-staging).*

systems is not uniform, and authors of this recommendation would favour the guidelines of a consensus conference held in 1997 (42), which form the basis for German and French national recommendations (41). A commonly used prognostic factor can also be specified, the Van Nuys Prognostic Index with three variables (size, grade/necrosis, closest margin; VNPI), and its improved, upgraded version, the University of Southern California/Van Nuys Prognostic Index (USC/VNPI) including age as a fourth variable (**Table 9**) (43). As shown in **Table 9**, the Van Nuys grading is a two-component two-tiered system distinguishing between high and non-high grade nuclei and for the latter category further scoring is based on the presence or absence of necrosis.

For invasive tumours, the presence or absence of peritumoral lymphovascular invasion (lymphatic and/or blood vessel invasion) should be reported.

Quantification of tumour-infiltrating lymphocytes (TIL), which can be performed on core-needle biopsy for PST, and from surgical specimens otherwise, may be a predictive and also a prognostic parameter when determining the effectiveness of (primary) systemic treatment. According to an international

TABLE 5 | Histological classification of breast tumours according to the fifth edition of the WHO classification (40).

Tumour group	Name	ICD-0	ICD-11
EPITHELIAL TUMOURS			
Benign epithelial proliferations and precursors	Normal (typical) ductal hyperplasia		GB20.Y
	Columnar cell lesions, including atypical columnar cell transformation (FEA, flat epithelial atypia)		GB20.Y
	Atypical ductal hyperplasia (ADH)		GB20.Y
Adenosis, benign sclerosing lesions	Sclerosing adenosis		GB20.Y
	Apocrine adenoma	8401/0	2F30&XH6YZ9
	Microglandular adenosis		GB20.Y
	Radial scar/Complex sclerosing lesion		GB20.Y
Adenomas	Tubular adenoma	8211/0	2F30.0&XH7SYZ9
	Lactating adenoma	8204/0	2F30.1&XH0W31
	Ductal adenoma	8503/0	2F30.2&XH4LZ4
Epithelial-myoepithelial tumours	Pleomorphic adenoma	8940/0	2F30.Y&XH2KC1
	Adenomyoepithelioma NOS	8983/0	2F30.Y&XH2V57
	Adenomyoepithelioma with carcinoma	8983/3	2C6Y&XH7TL5
	Epithelial-myoepithelial carcinoma	8562/3	
Papillary neoplasms	Intraductal papilloma	8503/0	2F30.2&XH4LZ4
	Papillary ductal carcinoma *in situ*	8503/2	2E65.2&XH4V32
	Encapsulated papillary carcinoma	8504/2	2E65.Y&XH9XV2
	Encapsulated papillary carcinoma with invasion	8504/3	2C6Y&XH0GT6
	Solid papillary carcinoma *in situ*	8509/2	2E65.Y&XH0134
	Solid papillary carcinoma with invasion	8509/3	2C64
	Invasive papillary carcinoma	8503/3	2C60&XH8JR8
Non-invasive lobular neoplasia	Atypical lobular hyperplasia (ALH)		
	Lobular carcinoma *in situ* (LCIS), NOS	8520/2	2E65.0&XH6EH0
	Classical LCIS		
	Florid LCIS		
	Pleomorphic LCIS	8519/2	
Ductal carcinoma *in situ* (DCIS)	Intraductal breast carcinoma, NOS	8500/2	2E65.2cXH4V32
Invasive breast carcinoma	Invasive carcinoma, NST	8500/3	2C61.0&XH7KH3
	Microinvasive carcinoma		2C61.0
	Invasive lobular carcinoma	8520/3	2C61.1&XH2XR3
	Tubular carcinoma	8211/3	2C60&XH4TA4
	Cribriform carcinoma	8201/3	2C60&XH1YZ3
	Mucinous carcinoma	8480/3	2C60&XH1S75
	Mucinous cystadenocarcinoma	8470/3	2C60&XH1390
	Invasive micropapillary carcinoma	8507/3	2C60&XH9C56
	Carcinoma with apocrine differentiation	8401/3	2C61&XH4GA3
	Metaplastic carcinoma	8575/3	2C6Y&XHORD4
Rare and salivary gland type tumours	Acinic cell carcinoma	8550/3	2C60&XH3PG9
	Adenoid cystic carcinoma (ACC)	8200/3	2C60&XH4302
	Secretory carcinoma	8502/3	2C60&XH44J4
	Mucoepidermoid carcinoma	8430/3	2C60&XH1J36
	Polymorphic adenocarcinoma	8525/3	2C60&XH5SD5
	Tall cell carcinoma with reversed polarity	8509/3	2C6Y
Neuroendocrine neoplasia	Neuroendocrine tumour NOS	8240/3	2C6Y&XH9LV8
	Neuroendocrine tumour Grade 1	8240/3	
	Neuroendocrine tumour Grade 2[a]	8249/3	
	Neuroendocrine carcinoma NOS	8246/3	2C6Y&XH0U20
	Neuroendocrine carcinoma, small cell	8041/3	2C6Y&XH9SY0
	Neuroendocrine carcinoma, large cell	8013/3	2C6Y&XH0NL5
FIBROEPITHELIAL TUMOURS, HAMARTOMAS	Hamartoma		
	Fibroadenoma NOS	9010/0	2F30.5&XH9HE2
	Phyllodes tumour NOS	9020/1	
	Phyllodes tumour, benign	9020/0	2F30.3&XH50P7
	Phyllodes tumour, borderline	9020/1	2F75&XH5NK4
	Phyllodes tumour, malignant	9020/3	2C63&XH8HJ7

(Continued on following page)

TABLE 5 | (*Continued*) Histological classification of breast tumours according to the fifth edition of the WHO classification (40).

Tumour group	Name	ICD-0	ICD-11
NIPPLE TUMOURS	Syringomatous tumour	8407/0	2F30.Y&XH9GB7
	Nipple adenoma	8506/0	2F30.Y&XH7GN3
	Paget's disease	8540/3	2E65.5&XH3E21
MESENCHYMAL TUMOURS			
Vascular tumours	Haemangioma NOS	9120/0	2F30.Y&XH5AW4
	Angiomatosis		2E81.0Z
	Common angiomatosis		
	Capillary angiomatosis		
	Atypical vascular lesions	9126/0	
	Postradiation angiosarcoma of the breast	9120/3	2B56.2&XH6264
	Primary angiosarcoma of the breast	9120/3	2B56.2&XH6264
Fibroblastic/myofibroblastic tumours	Nodular fasciitis	8828/0	2F30.Y&XH5LM1
	Myofibroblastoma	8825/0	2F30.Y&XH8JB0
	Desmoid fibromatosis	8821/1	2F75&XH13Z3
	Inflammatory myofibroblastic tumour	8825/1	2F30.Y&XH66Z0
Peripheral nerve sheath tumour	Schwannoma NOS	9560/0	2F30.Y&XH98Z3
	Neurofibroma NOS	9540/0	2F30.Y&XH87J5
	Granular cell tumour	9580/0	2F30.Y&XH09A9
	Granular cell tumour, malignant	9580/3	
Tumours of smooth muscle origin	Leiomyoma NOS	8890/0	2F30.Y&XH4CY6
	Leiomyosarcoma NOS	8890/3	2C6Y&XH7ED4
Adipose tissue tumours	Lipoma NOS	8850/0	2F30.Y&XH1PL8
	Angiolipoma NOS	8861/0	2F30.Y&XH3C77
	Liposarcoma NOS	8850/3	2C6Y&XH2J05
Other mesenchymal tumours and tumour-like lesions	Pseudoangiomatous stromal hyperplasia		GB20.Y
HEMATOLYMPHOID TUMOURS	Lymphoma		
	MALT lymphoma	9699/3	2A85.3
	Follicular lymphoma (NOS)	9690/3	2A80.Z
	Diffuse large B-cell lymphoma NOS	9680/3	2A81.Z
	Burkitt lymphoma NOS/Acute leukaemia, Burkitt type	9687/3	2A85.6
	Anaplastic large cell lymphoma associated with breast implant	9715/3	2A90.B
MALE BREAST TUMOURS	Epithelial tumours		
	Gynaecomastia		GB22
	Carcinoma *in situ* NOS	8500/2	
	DCIS		2E65.2&XH4V32
	LCIS		2E65.0&XH6EH0
	Paget's disease of nipple		
	Invasive carcinoma, NST	8500/3	2C61.0&XH7KH3
BREAST METASTASES			2E0Y&XA12C1
GENETIC TUMOUR SYNDROMES	*BRCA1/2*-associated hereditary breast and-ovarian cancer syndrome		2C65
	Cowden syndrome		LD2D.Y
	Ataxia-telangiectasia		4A01.31
	Li–Fraumeni syndrome, *TP53*-associated		
	Li–Fraumeni syndrome, *CHEK2*-associated		
	CDH1-associated breast cancer		
	PALB2-associated breast cancer		
	Peutz–Jeghers syndrome		LD2D.0
	Neurofibromatosis type 1		LD2D.10
	Polygenic component of breast cancer susceptibility		

[a]*The term "neuroendocrine tumour (NET) Grade 3" is not included in the WHO publication, although the principle was to harmonize the classification of neuroendocrine neoplasms with that used for other organs. Breast NET grade is determined according to the Nottingham grading scheme, which is different from the NET grading system used for other organs; Grade 3 has not been defined. Breast NET is defined as a malignant tumour. Breast NET is rare, so the prognosis of tumours classified in this category is unknown. (Altogether, the classification of tumours into NET, NEC or NST carcinoma with neuroendocrine differentiation is somewhat controversial, these tumours require individual and multidisciplinary approaches to avoid improper management. NOS, not otherwise specified; NST, no special type.*

TABLE 6 | Combined histologic grade (Nottingham) (6).

Tissue characteristic	Points
A. Tubule formation	
For the most part of the tumour (>75%)	1
To a moderate extent (10–75%)	2
To a small extent (<10%)	3
B. Nuclear pleomorphism	
Small (<1.5 × normal), regular, uniform nuclei, uniform chromatin	1
Moderately larger (1.5–2 × normal) nuclei with variability in size and shape, visible nucleoli	2
Large (>2 × normal) vesicular nuclei with marked variability, multiple nucleoli	3
C. Mitotic index (depending on the size of the field of view)	See table below

		Number of mitoses in 10 high magnification fields of view		
Field of view diameter in mm	**Field of view area in mm^2**	**Score 1**	**Score 2**	**Score 3**
0.40	0.126	≤4	5–8	≥9
0.41	0.132	≤4	5–9	≥10
0.42	0.138	≤4	5–9	≥10
0.43	0.145	≤4	5–10	≥11
0.44	0.152	≤5	6–10	≥11
0.45	0.159	≤5	6–11	≥12
0.46	0.166	≤5	6–11	≥12
0.47	0.173	≤5	6–12	≥13
0.48	0.181	≤6	7–12	≥13
0.49	0.188	≤6	7–13	≥14
0.50	0.196	≤6	7–13	≥14
0.51	0.204	≤6	7–14	≥15
0.52	0.212	≤7	8–14	≥15
0.53	0.221	≤7	8–15	≥16
0.54	0.229	≤7	8–16	≥17
0.55	0.237	≤8	9–16	≥17
0.56	0.246	≤8	9–17	≥18
0.57	0.255	≤8	9–17	≥18
0.58	0.264	≤9	10–18	≥19
0.59	0.273	≤9	10–19	≥20
0.60	0.283	≤9	10–19	≥20
0.61	0.292	≤9	10–20	≥21
0.62	0.302	≤10	11–21	≥22
0.63	0.312	≤10	11–21	≥22
0.64	0.322	≤11	12–22	≥23
0.65	0.332	≤11	12–23	≥24
0.66	0.342	≤11	12–24	≥25
0.67	0.352	≤12	13–25	≥26
0.68	0.363	≤12	13–25	≥26
0.69	0.374	≤12	13–26	≥27
0.70	0.385	≤13	14–27	≥28

Nottingham histologic grade	
Well differentiated, grade I	Scores 3 to 5
Moderately differentiated, grade II	Scores 6 to 7
Poorly differentiated, grade III	Scores 8 to 9

Auxiliary table for assessing the score based on mitosis index according to Chapter 6 of the European Guideline for Breast Cancer Screening (Quality assurance guidelines for pathology in mammographic screening) and the WHO tumour classification (6,40).

recommendation, only mononuclear cells/"round cells" in the stroma should be considered within the borders of the invasive tumour (**Table 10**) (44, 45). Based on the presence of TILs, a group of lymphocyte-predominant breast cancers (LPBC) can be distinguished (in which, in principle, there are fewer tumour cells than lymphoid stroma or lymphoid cells; this is indicated at a stromal TIL ratio higher than 50% or 60%). This type of cancer shows a higher rate of pathological complete regression after neoadjuvant treatment. TIL is mostly predictive of significant or complete regression in triple-negative and HER2-positive breast cancers (18, 46). Meta-analyses have shown that the amount of TIL is not only predictive of the effectiveness of PST (18) but also reflects the effectiveness of adjuvant treatment (47).

Assessment of Axillary Lymph Node Status

Physical and ultrasound examination of the armpit is part of patients' preoperative assessment, during which it is necessary

TABLE 7 | Nottingham prognostic index (NPI) (7).

*No lymph nodes involved	1
1–3 lymph nodes involved	2
>3 lymph nodes involved	3
Prognostic groups based on NPI value	
Excellent prognostic group (EPG)	2–2.4
Good prognostic group (GPG)	2.41–3.4
Moderate prognostic group I (MPG-I)	3.41–4.4
Moderate prognostic group II (MPG-II)	4.41–5.4
Poor prognostic group (PPG)	5.41–6.4
Very poor prognostic group (VPPG)	> 6.41

Tumour size (cm) × 0.2 + lymph node score (according to lymph node involvement, score: 1–3) + grade score (grade I–score 1, grade II—score 2, grade III—score 3).*

to distinguish between patients who are clinically metastatic, i.e., node-positive (including cases confirmed by axillary ultrasound, aspiration cytology, and possibly core biopsy) and non-metastatic, i.e., node-negative patients. For this reason, targeted sampling (mostly aspiration cytology, rarely core biopsy) is part of the preoperative assessment when clinical suspicion arises. As surgical procedures change, core needle biopsy sampling is expected to become more frequent, related to (clip, magnetic or radioactive seed) marking of metastatic axillary lymph nodes before PST; however, core needle biopsy is not a prerequisite for clip insertion, since this is inserted with a separate device and may be placed after fine needle aspiration, too. In addition to establishing the diagnosis of metastasis, a sample obtained from an axillary lymph node may also be suitable for the assessment of certain prognostic/predictive factors of the tumour (ER, PR, HER2, and Ki67).

Axillary Clearance Specimen Processing

All lymph nodes should be retrieved from the axillary fat for histological examination. Lymph nodes larger than 5 mm should be embedded, preferably cut into 2 mm thick slices, while those smaller than 5 mm should be embedded as a whole. From lymph nodes that are clearly metastatic macroscopically, embedding one single representative block is sufficient. It is advisable to choose a macroscopic slice in which extracapsular spread, if present, can also be identified. When performing the above, a methodology and marking should be used that enables reporting of the number of examined and metastatic lymph nodes at the end of the examination (e.g., staining, accurate recording of the number of lymph nodes per block if more than one lymph node is included in a block).

For axillary lymph nodes removed after PST, knowledge of the pre-treatment lymph node status and communication of this to the pathologist is essential. In addition to lymph nodes, small connective tissue masses, which are often only palpable, should also be examined. Routine use of cytokeratin immunohistochemistry in patients with lesions that suggest only scarring and regression is not warranted; however, for an HE finding suggestive of a tumour, it may help to assess the presence of residual tumour.

Sentinel Lymph Node

- For pathologists, a lymph node sent by a surgeon with such designation is considered a sentinel lymph node.
- Basic examination of sentinel lymph nodes is embedded histological examination.
- Broadly speaking, sentinel lymph node involvement by micrometastases (see TNM staging in **Table 4**) or otherwise occult metastases that can be detected only by using special techniques, have minimal prognostic value (48). Short-term results from surgical randomized studies of micrometastases do not support completion axillary lymph node dissection for such cases (49, 50), and according to international recommendations, systemic treatments are never based solely on the presence of micrometastases (47, 48). Therefore, it appears that there is no need for a processing of sentinel lymph nodes that is more thorough than the one suitable for the detection or exclusion of metastases larger than micrometastases (i.e., macrometastases). As a first approach, a negative sentinel lymph node sent to the pathology department should be processed in a way that allows to rule out the presence of macrometastases as reliably as possible. For this, it is sufficient to examine the HE-stained section of slices made in 2 mm increments. When needed (e.g., for uncertain HE finding of lobular carcinoma or for suspected malignant cells after PST), cytokeratin immunohistochemistry may be used as a complementary method. After PST, minimal residual tumour (even the presence of isolated tumour cells) will indicate axillary lymph node dissection (20), but the recommendations do not consider more extensive processing and routine immunohistochemistry necessary even in this setting (12). In the first approach, for metastatic lymph nodes, a minimal examination providing the most accurate information about the metastasis (e.g.,

TABLE 8 | Grading of *in situ* ductal carcinomas: as recommended by the DCIS Consensus Conference (1997) (42).

Low grade DCIS (Nuclear grade 1)	Monotonous (monomorphic) nuclei with a size of 1.5–2 RBCs or of a normal ductal epithelial cell. Chromatin is usually diffuse, finely distributed, nucleoli or mitotic forms are only rarely detected. Cells are usually located in a polarized form. (The presence of nuclei of the same size but pleomorphic character will exclude low grade).
Intermediate grade DCIS (Nuclear grade 2)	Nuclei do not fall into either nuclear grade 1 or nuclear grade 3 category, they are classified as intermediate.
High grade DCIS (Nuclear grade 3)	Marked pleomorphism of nuclei with a size >2.5 RBC or of a normal ductal epithelial cell. Usually vesicular nuclei, with irregular, coarse chromatin, with visible, often multiple nucleoli. Mitosis rate may be high.

DCIS grade should be determined based on the nuclear grade. In addition, the presence and nature of necrosis (zonal/comedo or spotty), cell polarization, DCIS pattern(s) (comedo, cribriform, micropapillary, papillary, solid, other) and possible heterogeneity of grade should be reported regardless of grade.

TABLE 9 | Assessment of DCIS prognosis: University of Southern California/Van Nuys Prognostic Index (43).

Scoring	1	2	3
Tumour size (mm)	≤15	16–40	≥41
Surgical margin (mm)	≥10	1–9	<1
Histological classification (grade)	Non-HG without necrosis	Non-HG with necrosis	HG
Age	>60	40–60	<40

With breast preservation, prognosis is good (low probability of recurrence) if the sum of scores is 4–6, moderate if it is 7–9, and poor if it is 10–12. HG: high grade (poorly differentiated). The significance of USC/VNPI, is that of an auxiliary tool for the selection of another treatment strategy after conservative surgery: cases with a high score (10–12) are candidates for mastectomy, whereas cases with a score of 7–9 for radiotherapy.

TABLE 10 | Recommendation for quantification of tumour-infiltrating lymphocytes (TILs) as recommended by the International TILs/Immuno-Oncology Working Group (44,45).

0. In terms of practice, TILs can be interpreted in several localizations. Recommendation applies to a quantitative estimation of the stromal TILs (sTILs) compartment; the term TILs is used synonymously with this. The following recommendation applies to invasive breast cancers
1. The % of TILs should be expressed as the percentage of stromal area occupied by mononuclear stromal inflammatory cells (including plasma cells and lymphocytes but excluding granulocytes) as compared to the total area of the tumour stroma.
2. TILs should be assessed within the borders of the invasive tumour, which includes the invasive front of the tumour (a 1 mm zone at the tumour margin).
3. Mononuclear cells a) beyond the tumour border (invasive front), b) around DCIS, c) around normal lobules, as well as areas that d) are artificially damaged, e) are necrotic, f) show regressive hyalinization and g) showing the site of the previous core needle biopsy should be excluded from evaluation
4. Analysis of a 4–5 micron thick section per patient, examined at × 200 or ×400 magnification is sufficient.
5. Full sections should be preferred to core needle biopsies, but only the latter can be evaluated for PST
6. The average TILs should be assessed in a section, and not the most intensively infiltrated areas, exclusively
7. Quantification of TILs as a continuous variable should be performed with the highest precision possible, which in daily practice means rounding to percentages, usually ending in 5 or 0
8. It should also be considered that lymphocytes typically do not form confluent cell groups, so small empty gaps between mononuclear inflammatory cells in the TIL-infiltrated stromal area (in the numerator of the proportion; the total intratumoural stromal area being the denominator) are acceptable, and they exist even with an upper limit of 100% for stromal TILs
9. No formal limits have been set. In addition to the semi-quantitative value of stromal TILs, a descriptive name, such as "lymphocyte-predominant breast cancer" (LPBC) may also be used, in which the number of lymphocytes is basically greater than that of tumour cells; by definition, a population of lympho-plasmacytes exceeding 50% or (according to another definition) 60% of the stromal area of interest, can be identified within the tumour.

histological examination of the section representing the largest dimension) will be sufficient.

- Pathological processing of sentinel lymph nodes can be tailored based on clinical picture and need: if axillary lymph node dissection is not planned in the first instance for patients with clinically negative axillary status in cases of sentinel lymph node involvement (51–54), then intraoperative examination is not useful. In other cases, intraoperative evaluation may also be required. The aim is to detect right away as many of the metastatic sentinel lymph nodes as possible, so that any axillary clearance that becomes necessary can be performed in one operative session, if possible. However, it should also be taken into account that intraoperative microscopic examinations are not able to identify all metastases; their sensitivity is low, especially for micrometastases. Both cytology and intraoperative frozen section histology are suitable for intraoperative examinations, but frozen serial sectioning of the entire lymph node is contraindicated. Based on a meta-analysis, the sensitivity of a frozen sections is approximately 10% higher than that of imprint cytology (55, 56). Validated assays based on quantitative reverse transcription polymerase chain reaction or loop mediated isothermal amplification are also suitable for intraoperative examination of metastases. (Most of these have been calibrated so that cases falling into the "isolated tumour cell" category are not classified as metastatic.) As a basic principle, a lymph node should not be used in its entirety for a poorer quality intraoperative examination.

Special Assessment of Prognostic and Predictive Factors (Steroid Hormone Receptors and HER2 Determination, Ki67)

The factors listed in this subheading are items that currently influence the treatment of breast cancer and need to be examined separately.

- Fixation of the fresh specimen should start as soon as possible: immediately or, for optimal receptor determination, no later than 30–60 min after excision, in 10% formalin kept in a refrigerator at 4°C, in a minimum of 5 times the volume of the specimen (57). If the material is not delivered to the pathology department within 2 h, it is advisable to store it in the fixative solution in a refrigerator at 4°C until delivery, with uniform formalin penetration, fixation without crusting, ensuring the best preservation of proteins (even phosphorylated potential signal path targets), and nucleic acids (58, 59). If the fresh sample cannot

be delivered from the surgical to the pathology department within an optimal time limit (maximum 60 min), vacuum packaging and storage at 4°C, followed by delivery within up to 16 h is a validated alternative (60). Efforts should in any case be made to refrigerate the fresh sample to 4°C and deliver it as such, since this takes priority over transport at room temperature or higher, with or without formalin (and regardless of vacuum packaging) (58, 59). Duration of fixation for core biopsies is a minimum of 6 h; for surgical specimens, in the case of 5–10 mm thick slices prepared before fixation, an optimal duration of 24 h and up to 72 h is recommended (57, 61). For optimal receptor assessment, sections prepared on adhesive slides as freshly as possible within a maximum of 3 days are recommended. If the immunostains are performed later, fresh sections may be stored at 4°C in a dark place, away from air as much as possible (e.g., in a slide storage box, in contact with each other) for at least 2 months without significant antigen/DNA loss, and it is therefore recommended that control sections are stored in the same way (62).

- If predictive and prognostic factors need to be assessed from a metastasis (body cavity fluid) or, in the absence of other specimen, from a fine needle aspiration sample, only a formalin-fixed smear or cell block may be used for HER2 immunohistochemistry to avoid the high false positivity that occurs with alcohol fixation (63, 64). In the assessment of prognostic and predictive factors from cytological samples, the highest concordance with histological samples was shown for formalin-fixed, paraffin-embedded cell blocks, so efforts should be made to use this. For a cell block, the pre-analytical phase should be standardized similarly to tissue techniques. Whenever possible, whether for fine needle aspirate or a body cavity fluid, samples should be fixed in 10% buffered formalin for a minimum of 6 h and a maximum of 48 h. Afterwards, the cell block method used should be followed, and then the cell block should be treated similarly to the histological specimen (65–68). Using cell block techniques, predictive markers can be reliably assessed under conditions similar to histological specimens (69).

The optimal method for steroid hormone receptor determination is immunohistochemistry. Laboratories examining prognostic and predictive markers using immunohistochemistry are expected to participate in an external quality control programme and achieve appropriate qualification for their performance, with particular emphasis on samples sent by the quality control centre. In the context of steroid hormone receptor (oestrogen and progesterone receptors, as well as androgen receptors) testing, "oestrogen receptor" (ER) usually refers to the alpha subtype. There is still insufficient prognostic or predictive experience with oestrogen receptor beta and androgen receptors (AR) to require their assessment, although AR may be requested for triple negative tumours. Tumours with a staining rate of 1% or more are considered positive (10), although there is no doubt that tumours with staining between 1 and 10% have lower hormone sensitivity (69, 70). In light of these, the estimated proportion of positive cells and the average intensity of staining should be specified in the report. Cases showing no staining and those with less than 1% staining are considered hormone receptor negative. According to the latest recommendation, cases with an ER positivity of ≥1 and ≤10% should be classified into a new diagnostic category of "low positive/weakly positive" [The low positive designation applies only to invasive carcinoma and ER, and is not used for PR or DCIS (71, 72)]. In such cases, the result may warrant additional steps (re-testing of controls, involvement of a second examiner, validated digital quantification, comparison with previous samples taken from the patient, re-testing on the same or an alternative block) and require additional comments. These comments could include for example: "The cancer in this sample has a low level (1–10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with low level (1–10%) ER expression but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment." There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER negative cancers. In the absence of internal tissue control (and only if the external tissue control is adequate), it may be mentioned that ER status could be more reliably verified on a sample containing internal tissue control, if required (71). A more accurate prediction of therapeutic effects is provided by the semi-quantitative rapid scoring system proposed below (Allred quick scoring (4); **Table 11**) (To avoid false negativity, it is advisable to choose a block that also has a non-tumorous epithelial element as an internal control. In its absence, or if based on the histological type or grade, a negative reaction is unlikely, it is recommended that it be repeated with adequate controls). Antibodies with IVD (*in vitro* diagnostic) labelling are preferred for assessment. Examination of a large number of samples in external quality assurance programmes (UK NEQAS and NordiQC) has shown that false negativity is mainly due to insufficient antigen retrieval (over-fixing), so in doubtful cases it is advisable to increase the epitope retrieval time by approximately 30%–50% (73).

- In practice, assessment of HER2 status is justified for invasive cancers; the test is based partly on the degree of HER2 protein over-expression (immunohistochemistry, IHC) and partly on HER2 gene amplification (*in situ* hybridization, ISH). A practical cost-effective approach, in line with international recommendations, is that samples evaluated as 3+ on immunohistochemistry represent a positivity that allows for targeted anti-HER2 treatment. To avoid false positivity in 3+ cases, where the histological type or grade contradicts this HER2 status [tubular carcinoma, mucinous carcinoma, grade I no special type (ductal) carcinoma], it is recommended to repeat at least the HER2-IHC

TABLE 11 | Assessment of oestrogen and progesterone receptors by Allred quick scoring (QS) system (4).

Average intensity	Points
Negative	0
Weak	1
Intermediate	2
Strong	3
Proportion of positive nuclei	**Points**
No	0
<1%	1
1–10%	2
10%–1/3	3
1/3–2/3	4
>2/3	5

The sum of the two subscores will give the total score. Possible values: 0, 2–8. (Response to endocrine therapy is expected for a score >2, and the response is expected to increase proportionally with the score). In theory, ER (PR) status can be Allred+ (Allred QS > 2) with <1% staining (<1% 2+, Allred QS 3 or <1% 3+, Allred QS 4), these are interpreted as negative. If recurrent or metastatic tumours are examined, steroid hormone receptor assessment should be repeated. Pathology departments performing predictive immunohistochemical tests are expected to participate in an external quality assurance programme and achieve appropriate qualification. The use of an external control tissue is recommended, and it is advisable to select a block for the immunohistochemical reaction that includes an internal control.

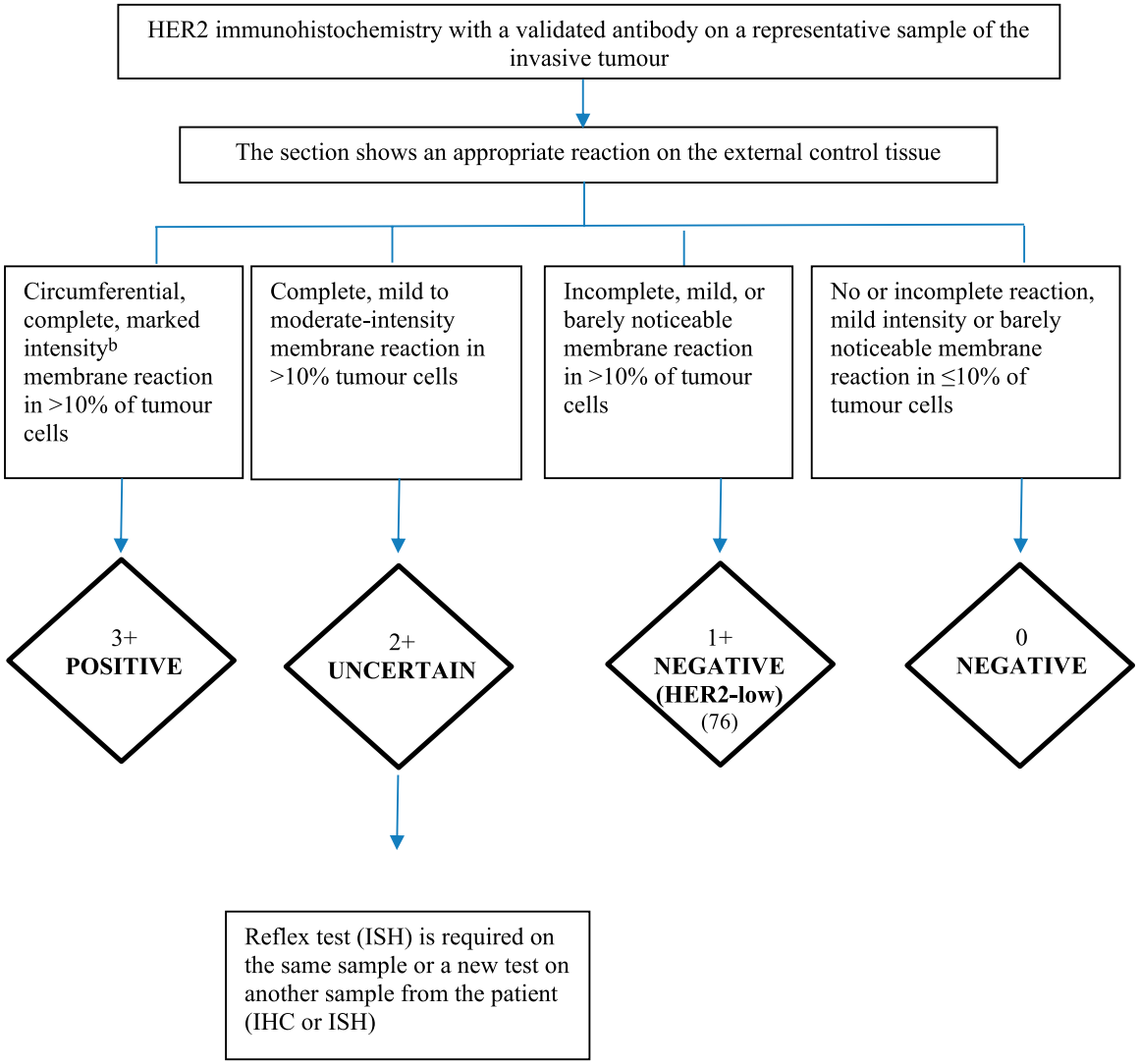
reaction. Samples rated 2+ by immunohistochemistry require further molecular testing, while samples rated 0 or 1+ based on HER2 immuno-staining, are considered negative for targeted treatment and prognosis. If classification based on immunohistochemical reaction is uncertain, an ISH test is justified. Rules and algorithm for determining HER2 status are shown in **Table 12** (14, 74–76).

- Of the HER2-ISH assays, fluorescence *in situ* hybridization (FISH) is the most widely used. For the evaluation of tumours with inconclusive results on IHC or FISH, the American Society of Clinical Oncology/College of American Pathologists has formulated 3 groups and recommendations for evaluation (**Table 12**) (14, 61). A suitable alternative to FISH can be the chromogenic (CISH) or the silver-enhanced (SISH) method. A combined method approved by the Food and Drug Administration for the combined assessment of HER2 amplification with chromogenic ISH (dual colour ISH, DISH) and of protein-level HER2 expression (IHC) is also available in the United States. This assay, known as GPA (gene-protein assay), may yield discordant results in some cells (77). IHC results seem to better reflect the efficacy of anti-HER2 treatment (78).
- More recently, clinical trials testing novel targeted drugs for breast cancers demonstrating a low level of HER2 expression/amplification require reconsideration of the HER2-negative vs. HER2 positive dichotomization. A category of HER2-low has been introduced for cases demonstrating IHC scores 1+ or 2+ without ISH evidence of amplification (76).

In addition to the mitosis rate, IHC testing of the Ki67 proliferation marker is the most common way of assessing proliferation. In such cases, the percentage of positive tumour cell nuclei relative to the total number of tumour cells should be reported, regardless of the intensity of the reaction. There are several suggestions and recommendations for quantification, as well as for limits serving to distinguish between high and low proliferation tumours. Until there are internationally accepted long-term recommendations, we recommend using an estimate with a 5% accuracy, when assessing the Ki67 labelling index for breast cancers. According to the 2015 St. Gallen recommendation on Ki67 labelling (69), cases of high and low proliferation are not separated by a cut-off point, but there is a value below which proliferation is clearly low (approximately 5%–10%) and there is a value above which it should be considered high (approximately 25%–30%), while in the zone between them, the Ki67 labelling index is interpreted as uncertain. At the latest, 2021 St Gallen consensus meeting, a majority of panellists (62%) agreed with the statement of the International Ki-67 Working Group that in women with ER-positive HER2-negative T1–2 N0–1 breast cancer a low Ki-67 ≤5% would not warrant chemotherapy, whereas a Ki-67 ≥30% would justify chemotherapy. In node-negative ER-positive PR-positive HER2-negative tumours, the majority (42%) voted for a Ki-67 of at least 30% for recommending chemotherapy. It should be noted that 36% of the panel members stated the threshold is not known. In ER-positive HER2-negative breast cancer, Ki-67 should be tested in all cases according to 61% of the panel, while 30% would only order Ki67 if chemotherapy is considered and a genomic signature is not available (79, 80). The Ki67 zone, which determines low and high proliferation, may be different for different implications (e.g., as an indication of adjuvant treatment, expected efficacy of neoadjuvant treatment, or estimation of actual efficacy as measured by interim core biopsies). If there is any doubt, a Ki67 reaction performed on a paraffin-embedded tonsil section fixed for 72 h (with external quality assessment granted) may demonstrate the suitability of the method and serve as a control (if there is uniform positivity of dark zone B cells in germinal centres and positivity in every 5th to 10th basal cell layer or every 2nd to 3rd supra-basal cell layer cell in the epithelium). Although Ki67 is one of the recommended prognostic factors, its assessment may be skipped if there is a high mitosis rate (e.g., twice the mitosis score required for mitosis score 3, when grading).

- In some tumours (thus far only triple-negative, metastatic breast cancers), assessment of PD-L1 has become widespread, and testing was recommended to be performed in the metastatic tumour, if possible. Based on evidence from a clinical trial (81), although SP142 is the antibody with the weakest performance among anti-PD-L1 antibodies tested (82), PD-L1 positivity determined by it may be an indicator of the efficacy of immunotherapy (atezolizumab) and it is currently a prerequisite for this treatment. The reaction can be

TABLE 12 | Assessment of HER2 tests[a] (14, 74–76).



NOTE. The issued report assumes that there is no inconsistency between histological type and HER2 status.[c] Unusual patterns of HER2-IHC reaction can also be seen, which are not covered by the above definitions. These are rare and should be interpreted mostly as 2+ (uncertain) cases. For example, in certain specific types of breast cancer, a lateral or basolateral, particularly intensive reaction may occur; these cases are interpreted as 2+ in the IHC response and it is not uncommon for them to show amplification with ISH. Another example is a complete, particularly intensive membrane positivity (heterogeneity) seen in ≤10% of cases. These cases are interpreted as 2+, but it is not uncommon to see different results in additional tumour samples.

Grouping based on HER2 (dual probe) ISH result

1. Group 1: POSITIVE, *HER2*/CEP17 ratio ≥2.0 AND mean *HER2* copy number per cell ≥4.0
2. Group 2: *HER2*/CEP17 ratio ≥2.0 AND mean *HER2* copy number per cell <4.0. Considered positive only if IHC is 3+
3. Group 3: *HER2*/CEP17 ratio per cell <2.0 AND mean *HER2* copy number ≥6.0. Considered positive only if IHC is 2+ or 3+
4. Group 4: *HER2*/CEP17 ratio <2.0 AND mean *HER2* copy number per cell ≥4.0 but <6.0. Considered positive only if IHC is 3+
5. Group 5: NEGATIVE, *HER2*/CEP17 ratio <2.0 AND mean *HER2* copy number per cell <4.0

(Continued on following page)

TABLE 12 | (*Continued*) Assessment of HER2 tests[a] (14, 74–76).

ISH groups	Biology	HER2/CEP17 ratio	Mean HER2 copy number	2018 ASCO/CAP recommendation
1	Classical HER2-amplified tumour	≥2	≥4	Positive
2	Chromosome 17 monosomy	≥2	<4	Negative (HER2-low if IHC 1+/2+; 76) unless HER2 IHC is 3+[d]
3	Co-amplification (previously chromosome 17 polysomy)	<2	≥6	Negative (HER2-low if IHC 1+; 76); unless HER2 is IHC 2+ or 3+
4	Borderline/uncertain	<2	≥4 and <6	Negative (HER2-low, if IHC 1+/2+; 76) unless HER2 is IHC 3+
5	Classical HER2 non-amplified tumour	<2	<4	Negative (HER2-low, if IHC 1+/2+ (76)

Summary of ASCO/CAP HER2 Professional Recommendation of 2018.

Cases rated 3+ are considered positive for targeted treatment, while those rated 2+ are considered uncertain, including cases showing strong membrane staining in <10% of cells. Cases rated 0 and 1+ should be considered negative. (F)ISH: this is mandatory in cases of uncertain HER2 status with IHC.

HER2-low category encompasses non-amplified IHC 1+ and 2+ cases, and accordingly the "non-positive" cases of ISH groups 2, 3 and 4 (76).

[a]Based on the latest (2018) ASCO/CAP recommendations (ASCO/CAP).

[b]Clearly visible at low magnification in a homogeneous, contiguous tumour cell population.

[c]HER2 positivity is virtually non-existent in the following tumour types:

Histological grade 1 NST carcinomas
Classical lobular carcinoma, oestrogen and progesterone receptor positive
Tubular carcinoma
Mucinous carcinoma
Cribriform carcinoma
Adenoid cystic carcinoma

[d]In the case of HER2 monosomy, there is clinical evidence, based on retrospective analysis, that these may respond to targeted treatment in the same way as HER2 positive tumours, suggesting that targeted treatment should be considered for this group (75).

HER2 testing should be performed on the surgical specimen in the following cases, even if this has previously been done on the core biopsy specimen:

if the core biopsy sample contained a small amount of tumour tissue or the invasive component of the tumour was visible only in the surgical specimen.
if the surgical specimen shows a high grade carcinoma not seen in the core biopsy specimen, or morphological heterogeneity or a different additional tumour nodule that was not represented by the core biopsy (30).
if it is suspected that a preanalytical error has occurred during the processing of the core biopsy sample.
if the HER2 assessment in the core biopsy sample yielded an uncertain result
if HER2 positivity in the core biopsy sample was heterogeneous in a tumour remaining after neoadjuvant treatment.

For recurrent or metastatic tumours, HER2 assessment should be repeated.

Heterogeneity of HER2

Definition of heterogeneity: an aggregated cell population consisting of amplified cells that make up >10% of tumour cells in the section examined. Individual amplified cells present in a mosaic-like, scattered distribution do not fall into this category. Cases as defined above are rare. Amplified and non-amplified areas should be examined separately, and *HER2* / CEP17 ratio and mean *HER2* copy number per cell in the two cell populations should be reported separately. The proportion of the amplified tumour cell population should be specified in the report. Cases with non-amplified and amplified areas should be considered HER2-positive. In the event of morphological heterogeneity, it is recommended to repeat HER2 testing on the surgical material (74).

Pathology departments performing predictive immunohistochemical tests are expected to participate in an external quality assurance programme and achieve appropriate qualification.

performed on a (core) biopsy or on surgical material. Due to the need for a costly infrastructure, this testing is only possible when there is an oncological indication and assessment is done in a few breast centres and not all countries. It cannot be done routinely yet. Positivity by IHC has a defined set of criteria, which for a tumour to be considered positive mainly requires that the proportion of the area occupied by PD-L1-positive "immune cells" in the evaluable stroma of the tumour is equal to or greater than 1%. Although we maintain the text relating to atezolizumab related PD-L1 testing, it must be mentioned that the United States Food and Drug Administration has suspended the accelerated approval of atezolizumab for metastatic triple negative breast cancer, and accordingly the National Cancer Collaborative Network (NCCN) guideline has removed the footnote advising testing for PD-L1 for the identification of candidates for atezolizumab therapy (83). At the time of writing, no related European Medicines Agency action has been noted, and atezolizumab is still a treatment option in Europe. Another clinical trial evidence supports the addition of pembrolizumab to chemotherapy in metastatic triple-negative breast carcinoma, but the biomarker test here involves the 22c3 antibody and a CPS (combined positive score) of 10 or above (84).

The Histopathology Report

Histopathology reporting of breast cancer can be done in a free text format, but it is recommended that a standard form be used, containing information about each of the essential elements (38). As an important part of the report, clinically relevant prognostic factors that can be assessed during the pathological examination should be specified. A short and clinically oriented summary of these factors is recommended, in accordance with the attached sample report. The range of relevant and

TABLE 13 | Overview of multigene expression-based/molecular prognostic tests (85–93).

Test	Methods	Number of genes/proteins tested	Role of patient group/test	ASCO/NCCN recommendation
OncotypeDX Tumour RNA	RT-PCR	21 genes (16 genes + 5 references genes)	ER/PR+, HER2-, pN0 ER/PR+, HER2-, pN1/ Estimation of the recurrence risk, assessment of the need for chemotherapy (predictive and prognostic)	strong
MammaPrint Tumour RNA	Microarray	70 genes	ER/PR+, HER2-, pN0 ER/PR+, HER2-, pN1/ Estimation of the recurrence risk, assessment of the need for chemotherapy (prognostic)	strong
Prosigna (PAM50) Tumour RNA	Microarray	50 genes + 5 references genes	ER/PR+, HER2-, pN0	intermediate
EndoPredict Tumour RNA	RT-PCR	12 genes (8 genes + 3 RNA references genes + 1 DNA references gene)	ER/PR+, HER2-, pN0 Assessing the need for chemotherapy, prolonged hormone therapy	intermediate
Germ cell mutation testing Non-tumour-derived DNA from blood	Sanger sequencing or NGS	BRCA1-2	Screening for hereditary breast cancer: Patients under the age of 40 years, significant family history of breast cancer, triple-negative breast carcinoma, history of ovarian cancer, susceptibility to PARP inhibitor therapy	strong
Gene panel test: hotspot mutations, amplifications, fusions; microsatellite instability (tumour DNA, RNA)	NGS, PCR, FISH, IHC	ESR1, PIK3CA, RB1, FGFR1, NTRK, microsatellite markers, MLH1, MSH2, MSH6, PMS2	Hormone therapy resistance, CDK4/6 inhibitor resistance. . .	Indication depending on clinical picture

independent prognostic factors, as well as predictive factors that are critical in terms of the treatment specified in the sample (Sample histopathology report), is currently considered sufficient. Other factors are either not sufficiently significant (e.g., necrosis, elastosis, etc.) or their independent prognostic value has not thus far been demonstrated (e.g., perineural invasion, ploidy, telomerase, cathepsin D, etc.). It should be noted that the Nottingham combined histological grade may also carry, with a few rare exceptions (e.g., adenoid cystic or mucoepidermoid carcinoma), prognostic information in more common special type breast cancers, so the use of grading is also recommended in the latter cases. A summary of the cytology report content is also provided along with the histopathology sample report.

MULTIGENE MOLECULAR TESTS

Over the last 2 decades, multigene tests based on molecular techniques have become more widespread. These may help in determining the nature of the oncological treatment to give (most often the need for chemotherapy or whether this can be omitted), or may be an indirect reference for choosing therapies by classifying tumours into molecular subtypes, and giving information on prognosis (recurrence). These commercially/provider-available tests examining the expression profile of specific genes are expensive, and only some of them are available with public funding, based on the recommendation of an oncology team. In some cases, when the indication for chemotherapy cannot be determined based on the conventional prognostic and predictive factors detailed above, such a test may be warranted. According to evidence resulting from the prospective randomized trial (TAILORx), OncotypeDx, based on the examination of the expression of 21 genes, is not only prognostic but also predictive of the efficacy of chemotherapy in ER+ HER2− pN0 breast cancers, and in general a recurrence score (RS) can be specified with which chemotherapy complementing endocrine therapy is not expected to have a significant effect, or above which chemotherapy has a survival benefit (85). The RxPONDER trial suggests that the same RS limit (25 or lower) identifies postmenopausal women with breast cancer who do not benefit from the addition of chemotherapy to endocrine treatment (86). Another test, EndoPredict, may be suitable for assessment of the efficacy of chemoendocrine therapy, based on a retrospective comparative study providing more limited evidence (87). A prospective randomized trial (MINDACT) evaluating the value of prognostic information provided by MammaPrint, a test based on examination of expression of 70 genes, concluded that among patients for whom risk assessment based on clinical and conventional pathological factors and gene expression led to contradictory results, genomic testing makes sense only in patients with clinically high risk. In some (nearly half) of these patients, chemotherapy can apparently be omitted based on a low genomic risk (88). In addition to the above, there are other studies on multigene prognoticators, of which the prognostic results are extrapolated to assess the presumed efficacy of chemotherapy administered in addition to endocrine therapy. The Prosigna (PAM50) test provides not only a molecular, gene expression profile-based classification of the tumor (luminal A, luminal B, HER2-enriched, basal like), but

TABLE 14 | Immunohistochemistry classification for therapeutic classification of breast cancers based on the recommendations of the St. Gallen Consensus Conference of 2015 (69).

Clinical classification	Notes
Triple negative	ER–/PR–/HER2–
Hormone receptor negative, HER2-positive	See criteria above
Hormone receptor positive, HER2-positive	See criteria above
Hormone receptor positive, HER2-negative: spectrum of luminal tumours	
Strong hormone receptor positivity, low proliferation, low tumour mass (luminal A-like)	Strong hormone receptor expression, low Ki67 labelling index. pN0-pN1, pT1-pT2
Intermediate	
Less hormone receptor positive, increased proliferation, high tumour mass (luminal B-like)	Lower hormone receptor expression, high Ki67 labelling index, ≥pN2, histological grade 3, extensive lymphovascular invasion, ≥pT3

Notes. ER positivity between 1% and 9% was considered uncertain by the St. Gallen consensus conference, rare tumors with this range of positivity have generally worse prognosis than those with higher range of ER positivity. The assessment of the Ki67 labelling index should be based on the average Ki67 values of each laboratory: e.g., if the median Ki67 labelling index is 20%, then a value below 10% is clearly low, a value of 30% or above is certainly high. As an update to this approach, the 2021 StGallen/Vienna Consensus proposed values >30% as an indication for chemotherapy in ER-positive tumours (79).

also provides a risk of recurrence (ROR) score, this may help in estimating the prognosis (89). Since this is a dynamically developing applied discipline, recommendations may change over time; it is most appropriate to choose the test in the light of existing evidence and clinical questions.

In addition to the above multigene, predominantly RNA-based assays, targeted therapies for breast cancer may require the assessment of additional DNA-based tests for gene mutations. Currently, germline BRCA1-2 mutation testing is the most common investigation for PARP (poly-ADP ribose polymerase) inhibitor treatment. Since this mutation analysis for breast cancer is performed on blood samples, a clinical geneticist should evaluate the results, and genetic counselling is required. Testing for gene mutations responsible for resistance to endocrine or CDK4/6 (cyclin-dependent kinase 4/6) inhibitor therapy either from tumour tissue or free circulating tumour DNA isolated from plasma are another group of multigene tests. Common guidelines for testing for these mutations have not yet been developed. Molecular tests are performed in specialized laboratories; our most important task is to maintain the quality of the sample by optimal fixation and processing conditions. This is particularly important in view of the fact that prognostic multigene tests are RNA-based, and RNA is more vulnerable than DNA. It is recommended that a multidisciplinary team decides whether these tests are to be run. **Table 13** provides a brief overview of the currently most widely used multigene tests and examinations of hotspot mutations required for targeted therapies (85–93).

Multigene testing methods (comprehensive genomic analysis) in which a potential resistance mechanism and/or therapeutic target is sought based on tumour-specific abnormalities may also be used, although these methods are used rarely because of the versatility of therapeutic options in breast cancer (94). Multidisciplinary decision-making is also crucial in this respect. In rare cases, molecular testing may also be performed to support a diagnosis (e.g., detection of ETV6-NTRK3 translocation typical of secretory carcinoma).

Use of tissue markers (the old-fashioned method to insert foreign tissues, generally from cadavers or benign surgeries, for either identification or orientation purposes) endangers the effectiveness of molecular tests, and therefore this traditional way of identifying and orienting the sample "in the 21st century era of targeted molecular diagnostics and modern patient rights, is a completely obsolete and unacceptable practice and should therefore be abandoned" (95).

Liquid biopsies are suitable for targeting circulating tumor cells (CTC) or circulating tumor DNA (ctDNA). Fields of application include 1) initial detection of oncogenic and targetable mutations, 2) response monitoring: under successful therapy, decrease of cell-free DNA (cfDNA) and ctDNA levels in blood; 3) identification of (actionable) resistance mutations in patients under therapy. One of the possible mechanisms for resistance in ER+HER2-cancers might be due to the dysregulation of phosphoinositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signalling pathway (96). Using blood components for liquid biopsies has become important in assessing *PIK3CA* mutations in ctDNA in breast cancer patients. Multiple techniques have been employed to isolate and analyse breast cancer ctDNA with high sensitivity and specificity (97). Without additional invasive testing, analysis of ctDNA in metastatic breast cancer for the presence of PIK3CA mutations have been successfully used in clinical oncology. Of several methodologies employed for *PIK3CA* mutation detection from liquid biopsies, digital droplet PCR has been proposed as the most sensitive approach which can detect mutations in ctDNA even in the non-metastatic setting (98). This allows timely follow-up, potentially overcoming spatial and temporal heterogeneity of tumour. Liquid biopsies can be analyzed in different settings, including pathology laboratories.

IMMUNOPHENOTYPE—"SURROGATE" TUMOUR TYPES

Since molecular subtypes of breast cancer were first described, there has been a growing need for pathologists to classify tumours, based on the pattern of immunohistochemical stains used in the everyday diagnosis of breast cancer, into surrogate subtypes that approximately reflect molecular subtypes. According to the recommendations of the St. Gallen

Consensus Conference in 2015 (69), triple-negative and HER2 groups are well defined among oestrogen receptor negative tumours, along with the luminal A-like oestrogen receptor positive cancers. But a significant group of hormone receptor positive tumours (called "luminal B-like") is very heterogeneous and difficult to define. The latter group includes tumours with low steroid hormone receptor expression, increased proliferation, and/or concomitant HER2 positivity. The 2013 and 2015 St. Gallen recommendations form the basis for this classification (69, 70), which is shown in **Table 14**; the content of the table has been valid since then. However, it should be noted that with proper definition of what each surrogate subtype means, it is not a mistake to simply describes the tumour in question with the phenotype (e.g., ER+ HER2+), as this will be understood. However, it is not recommended to classify as "luminal A" any tumour that, according to IHC, appears to be luminal A-like. Luminal A, luminal B, basal-like, "HER2 enriched" types are based on a gene expression profile; in addition to their definition, a prognosis-related score (ROR, risk of recurrence) can also be given.

CLINICAL TRIALS—ROLE AND DUTIES OF THE PATHOLOGIST

With the acceleration of targeted drug development, more and more patients are being treated in clinical trials, in which tumours are most often re-examined, or a target molecule or biomarker needed for treatment is assessed in a central laboratory. In such cases, cooperation with the pathologist diagnosing the tumour is required. A prerequisite for cooperation is that the pathologist is involved in the clinical trial, as the specialist creating the report serving as the basis for enrolment; as such, they should be informed of the details and objectives of the trial and their participation should be part of the contract. Preferably, the pathology department should be contracted by the study sponsors, to inform the participating pathologists about trial goals and material requirements as well as to ensure proper reimbursement of trial-related procedures. The specimen specified in the protocol must be released by the pathologist under the specified conditions and the delivery/dispatch of the block (or the requested specimen) should be documented. A similar situation may arise with regard to sample selection for multigene expression tests. For a limited amount of tumour tissue, division of the sample should also be considered.

THE PATHOLOGISTS' ROLE IN THE MULTIDISCIPLINARY TEAM

The diagnosis and treatment of breast cancer is a multidisciplinary collaboration between different medical and paramedical professionals. As mentioned before, the diagnosis of breast cancer and its differential diagnosis requires radiopathological and clinicopatholgical correlation. Adjuvant, neoadjuvant and palliative therapy related decisions are founded on prognostic and predictive markers, identified target molecules determined by pathologists. The interpretation of these results is not always straight forward, and communication by solely reports may lead to misunderstanding and harm to the patient. This is why it is expected that pathologists present their findings at the multidisciplinary tumor boards, interpret any limitations and take part in the decision-making process.

CONCLUSION—OBJECTIVES TO BE ACHIEVED IN THE FUTURE

As a conclusion to the text on pathology, here are some of the recommendations proposed by the expert panel, the implementation of which requires policy support, but which may contribute to a higher standard and better quality of professional practice, performed under better circumstances.

In the recommendations above, quality assurance is mentioned in two aspects, namely: an endeavour for cytology laboratories establishing the diagnosis; and a requirement for pathology laboratories involved in predictive immunohistochemistry. In the future, it seems to be a realistic goal that all pathology units involved in the screening and diagnosis of breast cancer should certify their professional competence using external quality control. Generally speaking, however, pathology laboratories should be prepared to achieve a higher level of quality, the elements of which are included in the requirements of ISO 15189 (99). The new *in-vitro* diagnostic regulation (Regulation (EU) 2017/746; IVDR) will come into full effect after a transition period ending in May 2027. This EU regulation replaces the directive 98/79/EC of the European Parliament on *in vitro* diagnostic medical devices (IVDD). The implementation of the IVDR has significant impact on medical laboratories, including pathology laboratories. Accordingly, laboratories will have to be accredited according to standards ISO 9001 or 15189.

- In addition to the technological external quality control indicated above, there is justification for setting up a centrally organized diagnostic (and reporting) programme for pathological units involved in breast cancer screening and diagnosis, in order to improve and ensure compliance, with the necessary infrastructure and financial resources.
- It would be appropriate to install specimen mammography devices in high throughput breast diagnostic pathology departments (the EUSOMA recommendation of 150 cases/year may be relevant here, see under "Non-operative diagnostics (preoperative or pretreatment biopsy diagnosis)".
- In line with the panel of radiology experts, we recommend that if an expert is involved in the diagnosis or false diagnosis of breast cancer in case of suspected error (e.g., legal dispute, claim for compensation, etc.), the expert should be a person with documentable experience in this field. Non-pathologists and general pathologists who examine small numbers (<100 per year) of cases and

have no experience in evaluating samples obtained from screening should not be accepted as experts. In order to give an opinion, an expert must simulate a real-life situation (they should not analyse the appropriateness of preoperative diagnosis and therapeutic decision retrospectively, with the knowledge of the detailed results of all investigations and surgical-histological reports). It is recommended that the expert form an opinion only on the basis of the information available at the time of the decision(s) contested in the dispute/lawsuit, evaluating the case in question together with several similar, anonymised cases.

- Development and investment in the field of digital pathology are also necessary. The possibilities of these developments are multifold and include teaching, quality control, consultation, morphometry, image analysis; and digital material is the *sine qua non* of artificial intelligence-based diagnostic, predictive algorithms.

This is part 2 of a series of 6 publications on the 1st Central-Eastern European Professional Consensus Statements on Breast Cancer covering imaging diagnosis and screening (100), pathological diagnosis (present paper), surgical treatment (101), systemic treatment (102), radiotherapy (103) of the disease and related follow-up, rehabilitation and psycho-oncological issues (104).

AUTHOR'S NOTE

The consensus document contains product placement without the intention of advertising. Each complex molecular test is unique, and although these can be described without indicating their name (for example with the number of genes tested), not everyone will necessarily understand what this refers to. For this reason, and adopting the practice used in some of the source works, the tests are listed under their trade name.

AUTHOR CONTRIBUTIONS

GC drafted the manuscript. All authors have complemented this with parts related to their field of expertise, the final content was discussed at the 1st Central and Eastern European Academy of Oncology organized consensus conference. All authors have reviewed the manuscript, taken part in its revisions and approved the final version submitted.

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CONFLICT OF INTEREST

Author BJ was employed by the company Medserv Kft.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.por-journal.com/articles/10.3389/pore.2022.1610373/full#supplementary-material

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Modern Breast Cancer Surgery 1st Central-Eastern European Professional Consensus Statement on Breast Cancer

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This text is based on the recommendations accepted by the 4th Hungarian Consensus Conference on Breast Cancer, modified on the basis of the international consultation and conference within the frames of the Central-Eastern European Academy of Oncology. The recommendations cover non-operative, intraoperative and postoperative diagnostics, determination of prognostic and predictive markers and the content of cytology and histology reports. Furthermore, they address some specific issues such as the current status of multigene molecular markers, the role of pathologists in clinical trials and prerequisites for their involvement, and some remarks about the future.

Keywords: breast cancer, surgery, consensus statement, oncoplastic surgery, oncology

INTRODUCTION

As part of the uptodate multidisciplinary treatment of breast cancer, organ specialized onco-surgery, breast surgery has evolved in many ways over the past decades. The most important causes of this progession are the evidence based clinical science, the biological concept of cancer treatment, the tendency of early diagnosis thanks to populational breast screening programmes and the wide spread of breast cancer awareness, the technological advances in diagnosis, pathology, molecular genetics,

pharmacology, radiotherapy and surgery, the quality assured centralization of breast cancer care, and the increased importance of rehabilitation and quality of life. In breast cancer surgery, the principle of minimally effective treatment instead of maximally tolerable treatment has become basic principle and practice.

Up to date surgical therapy for breast cancer will be determined by increasingly precise diagnostic and tumor localizing methods as well as increasingly effective oncology treatment procedures. Organ preserving surgery in combination with primary systemic treatments and the application of oncoplastic principles have become widespread. Sentinel lymph node biopsy is a primary approach in the surgical treatment of the clinically negative axilla, and the indication for axillary lymph node dissection has further decreased by the contribution of regional radiotherapy, medical treatment and targeted axillary surgery. Hereunder we summarise our recommendations on the surgical treatment of breast cancer based on the content of the fourth Hungarian Breast Cancer Consensus Conference as the first Central Eastern European Consesnsus Statement on Breast Cancer Surgery (1) and considering the latest international studies and professional recommendations (2–9).

SURGICAL TREATMENT OF INVASIVE TUMOURS

The purpose of surgical treatment is to ensure locoregional tumour control, as well as a precise assessment of the locoregional tumour stage. Besides the clinical stage, the biological behaviour of the tumour should also be considered when choosing surgical treatment. When providing surgical treatment for early-stage breast tumours, breast-conserving surgery should be pursued, if there is no objective contraindication. When planning breast-conserving surgery, the cosmetic results of the procedure, patient's preference and patient's future quality of life should also be considered. Without good or acceptable cosmetic outcomes, there is no point in breast conservation (10). The informed patient's opinion is also always taken into account when choosing optimal type of surgery. For unfavourable tumor to breast volume ratio, or locally advanced disease and/or cases with lymph node metastases, the possibility of neoadjuvant oncology treatment should be considered (see primary systemic treatment).

Criteria for Breast-Conserving Surgery

- Tumour of clinical stage I or II.
- Tumour size: solitary tumour (T1, T2); favourable ratio of healthy breast tissue/tumour volume, tumour location, optimal resecability. If optimal or acceptable cosmetic results cannot be achieved with conventional breast-conserving surgery, oncoplastic surgery should be considered (see oncoplasty), while taking into account the patient's prefernces (10). Assessment of breast parenchyma and tumour volume using the digital data from the diagnostic contrast enchanced MRI may help in selecting the type of surgical technique.
- Breast-conserving surgery can also be performed after primary systemic treatment. Neoadjuvant treatment can be used to reduce the size of the primary tumour (downsizing) so that the patient may become a candidate for breast-conserving surgery (see primary systemic treatment).
- Lymph node status: N0, N1, no distant metastases: M0 (relative—oligometastases).
- Appropriate adjuvant radiotherapy is provided and accepted by the patient after adequately informed about the adjuvant treatment.
- Appropriate professional, local radiological background is provided for preoperative tumour marking and localisation, intraoperative specimen mammography or ultrasound scanning.

Contraindication

- Unfavourable ratio of tumour to breast volume (which does not provide adequate oncological/cosmetic results even with oncoplastic techniques).
- Local recurrence or a new primary tumour after previous breast-conserving surgery (if no additional breast irradiation is possible).
- Extensive and/or multicentric ductal carcinoma *in situ* (DCIS) and invasive tumour (see chapter on DCIS, special considerations).
- Inflammatory breast cancer or mastitis carcinomatosa.
- Multiple malignant lesions (>2 lesions, in different breast quadrants, see special considerations).
- Tumour in a previously irradiated area (if no further irradiation is possible).

Relative Contraindication

Breast-conserving surgery can be performed under certain conditions:

- Multifocal or multicentric lesions (see special considerations).
- Tumour larger than 50 mm (tumour can be reduced with neoadjuvant treatment and/or it can be removed by oncoplasty and a suitable cosmetic/oncological result can also be achieved).
- Tumour located just under the nipple: for breasts of appropriate sizes, a so-called central quadrantectomy or historicaly: cone resection is possible, with sparing of the nipple-areolar complex, see special considerations: skin involvement (nipple-areolar complex) or negative coring specimen taken from the nipple, cannot be confirmed (intraoperative histological examination). However, presence of axillary lymph node metastases, tumour of grade 3, presence of lymphovascular invasion, and triple-negative or HER2-positive tumour may pose a higher risk.
- Mutation of the BRCA genes or other genes with high penetrancy (PALB2, TP53) mutation (see juvenile breast cancer) (2, 4, 5, 11).

- In cases of BRCA 1, 2 positivity, modern mastectomy as well as prophylactic removal of the contralateral breast should also be considered, with immediate or delayed-immediate reconstruction if required (12).

Special Considerations for Breast-Conserving Surgery

The success of breast-conserving surgery (i.e., how chances of local recurrence can be minimized and cosmetic outcomes improved) is influenced by several factors. The choice of surgical treatment (breast conservation vs. mastectomy) requires careful consideration and planning in cases of multifocal (MF) or multicentric (MC) breast cancers. In both cases, there are multiple cancer focis in the same breast. In MF cases, there are at least two invasive/*in situ* (DCIS) tumours within the same breast quadrant (or breast lobe), separated by non-involved/healthy breast tissue, while in MC cases, malignant foci are located in different breast quadrants (or breast lobes). Classification is important from a surgical point of view, too: multicentric tumours can usually only be removed via two separate incisions during conventional breast-conserving surgery, while multifocal tumours can be removed through one incision. Nowadays, by choosing the right oncoplastic breast conserving technique and with sufficient surgical experience, and also using precise localization techniques, MF tumours and (less frequently) MC tumours can be removed with an intact margin, should the size of the breast allow. An important prerequisite is an accurate preoperative and/or intraoperative diagnosis, of which contrast enchanced MRI scanning (that may detect new foci) and specimen mammogram/ultrasound are mandatory parts. If these criteria are met, a higher local recurrence rate can be reduced to an acceptable level (13, 14). However, for multifocal or multicentric breast cancers, breast-conserving surgeries cannot be considered routine procedures. In each case, malignant foci detected via imaging techniques should be confirmed by targeted sampling, since malignancy is pathologically confirmed in only 96%, even in cases with the highest probability (BI-RADS 5). Foci suspected of malignancy, but which are not available for biopsy (e.g., in the absence of MRI-guided sampling), should be evaluated by onco-team decision.

Oncoplastic Breast-Conserving Surgery and Modern Mastectomies

Oncoplastic breast surgery is an essential part of the multidisciplinary treatment of breast cancer, combining oncological and reconstructive surgical techniques with the necessary experience and effectiveness. The aim of oncoplastic breast-conserving surgery is to ensure the best possible cosmetic outcome in addition to oncological radicality, by remodelling the remaining breast parenchyma (volume displacement) or replacing missing ones by autologous flaps or implants (volume replacement). In 2009, oncoplastic breast surgical techniques were endorsed by the profession at the St. Gallen Consensus Conference (15).

Oncoplastic breast-conserving surgery involves oncological surgical procedures that require special surgical and plastic surgical (reconstructive plastic surgery) skills and experience (16). Besides outstanding cosmetic results, it allows removal of up to 20–50% of the breast (Level I and II oncoplastic techniques). Some techniques may require immediate or delayed contralateral symmetrisation. These oncoplastic surgical techniques are able to reduce the rate of microscopically involved surgical margins, their rate of morbidity is not higher than those seen with traditional breast-conserving surgeries, and they neither delay adjuvant multidisciplinary treatments, nor complicate oncological follow-up investigations on the long term. However, compared to traditional breast-conserving surgery, such techniques require a longer surgery time (17, 18).

Accurate marking of the tumour bed with clips is essential in oncoplastic surgery, not only for the purpose of radiotherapy planning, but also for the purpose of any local re-excision.

Overall, the oncological outcomes of oncoplastic surgical techniques are comparable to those of traditional breast-conserving surgeries and mastectomies; however, available long-term oncological outcomes are still with limited evidence (1, 5, 17, 19–22).

Skin-sparing mastectomy (SSM) is a type of mastectomy with removal of the nipple-areolar complex (NAC) and limited removal of periareolar skin with immediate/delayed-immediate breast reconstruction. This method can be primarily used for the surgical treatment of extensive ductal carcinomas *in situ* (DCIS), invasive tumours that do not infiltrate the skin, but located close or in the nipple or NAC, especially for centrally located tumours that deform and invert the nipple and areola or M Paget disease. There are no clear international or national recommendations regarding the absolute or relative indications of SSMs. For pathological assessment, examination of the so-called anterior (skin-facing) resection margin is important.

In nipple-sparing mastectomy (NSM), the entire skin of the breast is spared, while in areola-sparing mastectomy (ASM), the nipple is removed along with the parenchyma (23, 24). Surgeries can usually be performed via an incision made in the inframammary fold or in radial direction with or without periareolar extension (e.g., hockey stick incision, batwing etc.), in combination with immediate/delayed-immediate breast reconstruction. Marking of the direct retromammillary gland area for pathological examination, and intraoperative frozen section or postoperative histological examination of the retro-/intramammillary tissue as a separate specimen is an essential part of the method. If tumour is confirmed by the postoperative histology, removal of the nipple with or without the areola is required, which is most often easily carried out even in an outpatient setting. The indication range of NSM has widened, being oncologically equivalent to SSM, but yielding significantly better cosmetic results if there is careful patient selection and immediate/delayed-immediate reconstruction (Evidence II.B) (6, 23). Skin reducing NSMs (SRNSM) are endorsed surgical techniques with adequate radicality and acceptable morbidities, necessitating special surgical experience (25).

SSM/ASM/NSM surgeries are not surgically equivalent to early or classical subcutaneous mastectomy which was

routinely performed by leaving a substantial amount of glandular tissue.

Surgical Resection Margin

Removal of an invasive tumour is oncologically appropriate only if resection margins also prove to be tumour-free on pathological examination (there are no tumour cells within the ink-stained margin). In addition to unifocal tumours, the above recommendation is also considered acceptable for multifocal tumours, following the St. Gallen Consensus Conference of 2019 (7).

Further extension/increase of an intact resection margin is not justified, nor in young patients (<40 years) either in the presence of an extensive intraductal component, in invasive lobular carcinoma or in tumours with unfavourable biological properties. However, in some individual cases with intact margins, re-excision may be justified as defined above (e.g., in multifocal lobular cancers, where the tumour is significantly larger than assessed during preoperative diagnosis and its foci are very close to the stained surgical margin, though there is no ink on them).

For DCIS, both the American NCCN (National Comprehensive Cancer Network; 4) and the European ESMO (European Society of Medical Oncology) recommend achieving an intact resection margin of 2 mm (4, 6).

Intraoperative specimen mammography or ultrasound scanning may also be used to achieve an intact resection margin. In each case, exact orientation (e.g., lateral, medial, superior) of the removed breast specimen is required. Marking the base and walls of the tumour bed with 7marker clips/markers is essential. Three markers are placed to the base of the tumor bed while other 4 one to the parenchyma pillars/walls (posterior, lateral, medial, superior, inferior margins).

Pathological report (macroscopic, microscopic) should include information on the integrity of resection margins. If resection margins are involved, localization and nature of involvement (invasive or *in situ* foci, focal or broad/massive) should be described in millimeters.

It is also important to compare preoperative and intraoperative imaging and pathological investigations.

If the resection margin is positive, re-excision is required (usually once), or if re-excision is not possible and/or in case of or positive margin in re-excision specimen, mastectomy is recommended. Precise orientation and detailed surgical documentation of the tissue removed during re-excision is required. Description of macroscopic and microscopic surgical margins in the pathology report is also justified. If the posterior resection margin is affected and excision has also removed the fascia of the pectoralis major muscle (which was documented in the surgical description), no additional excision is required, only additional boost radiotherapy to the tumour bed. In addition, classical lobular carcinoma *in situ* (LCIS)/lobular neoplasia within the surgical margin is not an indication for re-excision (2–4, 26). However, both pleomorphic and possibly florid variants of LCIS have poorer biological behavior (27, 28); therefore, microscopical complete excision is recommended when the resection margin is involved (see below).

Non-Palpable Breast Tumours

For non-palpable breast tumours or lesions, preoperative marking is required in all cases. Both classical hook-wire marking and Radioguided Occult Lesion Localization (ROLL), or any other validated methods (Magseed, SaviScout etc.) are suitable for marking and removing non-palpable malignant or suspected malignant lesions. Ultrasound-assisted breast surgery significantly increases the possibility of tumor-free margins and therefore reduces the risk of reoperations (29–31). Several clinical studies have shown that ROLL (localization of non-palpable lesions) technique allows for a more accurate, cosmetically better excision, and that one-session sentinel lymph node biopsy (SNOLL technique) is easier to perform (29–31). Based on the above, hook-wire marking method could be recommended as a first choice for removal of large microcalcifications (DCIS); radial scars and complex sclerosing lesions, where a sentinel lymph node biopsy is not planned.

For invasive tumours, the ROLL technique is primarily used, as it is also suitable for marking sentinel lymph nodes. During surgery, both the tumour and the sentinel lymph node are removed using a hand-held gamma probe. It is mandatory to mark the tumour bed with clips (at least 7 clips) for the accurate adjuvant radiotherapy. Orientation of the removed specimen and specimen mammography/radiography or ultrasound scanning (see surgical resection margin) are also an essential part of the surgery. When choosing the method (ROLL vs. hook-wire marking or other methods like magnetic seeds etc.), the experience of the team (radiologist, surgeon, pathologist) should also be considered (29–31).

Surgical Treatment of the Axilla

Axillary surgery continues to play an important role in the treatment of invasive breast tumours (1): it provides information on the stage and prognosis of breast cancer and (2) provides regional tumour control. For early breast cancer, axillary surgery is also consistent with trends towards less extensive surgical treatments.

Following clinical axillary ultrasound scanning (AXUS) and ±aspiration cytology (FNAC) or core biopsy, sentinel lymph node biopsy (SLNB) (evidence 2.a) remains the standard axillary staging method for a lymph node-negative (cN0) breast cancer. This method allows reliable and accurate staging in patients with early breast cancer (1–3) and results in lower morbidity than for conventional axillary lymph node dissection (or axillary block dissection) (ALND). Based on the results of several prospective randomized, multicentre studies conducted over recent years (4, 5, 11–14), the indication for ALND has been narrowed down and axillary radiation therapy has become an accepted therapeutic alternative (under certain conditions) (evidence 2.a) (14, 32).

In concordance with the extensive use of primary systemic therapies (PST) in cN positive cases and with the high rate of becoming cN0 after the effective neoadjuvant systemic treatment new methods of targeted axillary surgical care is on the way of being validated and endorsed. New expressions like the targeted lymph node biopsy (TLNB) have been introduced in the literature, which means the selective removal of initialy

metastatic lymph node(s) marked with special clips and markers before neoadjuvant therapy or the phrase of targeted axillary dissection (TAD) which is a combination of TLNB and SLNB (33).

SenTa, a prospective multicenter study, showed that TAD minimizes the false negative rate of SLN after neoadjuvant chemotherapy in patients with node positive breast cancer, but detection rate of clipped lymph node was only 86.9% (34).

The multidisciplinary onco-team should decide on the need for and the nature of further treatments, taking into account the final histological results of the SLNs, the type of surgery, biological behaviour or molecular subtype of the tumour, and the patient's opinion.

Technical Considerations for Sentinel Lymph Node Biopsy

SLNB is usually performed in conjunction with removal of the primary tumour. If the breast tumour was previously removed and the presence of an invasive/microinvasive tumour has been subsequently confirmed, a sentinel lymph node biopsy has to be performed in a second session.

Currently, two methods are most commonly used to remove sentinel lymph nodes (6): dye labelling (patent blue) and (7) isotopic labelling (colloidal albumin labelled with ^{99m}Tc).

Over the past years, several alternative methods have been introduced for sentinel lymph node biopsy, such as fluorescent marking with indocyanine green (ICG) and magnetic marking with nanocolloids containing iron oxide (superparamagnetic iron oxide, SPIO; see the chapter on new methods for sentinel lymph node biopsy).

Identification rate and sensitivity of the isotopic labelling method is significantly higher than for blue dye labelling. The so-called double labelling is the most sensitive method (the identification rate of lymph nodes is 92% on average, while false negative rate of lymph node identification in less than 7% of cases) (35) and it is therefore currently considered an acceptable standard procedure (36, 37). Dye marking can be used as a salvage method, for example following negative lymphoscintigraphy after ROLL labelling. For isotopic labelling, especially in the case of repeated SLNB performed after previous axillary intervention, it is also important to perform a preoperative lymphoscintigraphy to evaluate the projection of sentinel lymph nodes and lymphatic drainage. During an SLNB procedure, in addition to the active lymph node(s) accumulating the isotope, any palpable, non-accumulating lymph nodes that are suspected to be metastatic lesions should also be removed and accurately labelled as non-SLN lymph nodes for the pathologist.

Removal of sentinel lymph nodes adjacent to the internal mammary artery is possible; staging can be refined with this procedure, but the result has little effect on further treatment; its routine use is therefore not justified (32).

Indication for Removal of Sentinel Lymph Nodes

- T1-T2 tumours.
- Clinically and radiologically (US) negative axilla, (there are no axillary lymph nodes suspicious of metastasis, or, if present, suspicion is not confirmed by evaluable (non-C1) pathological examination (guided aspiration cytology or core biopsy).
- After neoadjuvant (primary systemic) treatment (PST) if presence of axillary metastases was not confirmed prior to treatment.

Sentinel Lymph Node Biopsy in Other Special Cases

- Multicentric and multifocal lesions (20).
- Tumour size T3.
- After previous axillary surgery or breast augmentation.
- Male breast cancer.
- During pregnancy, using a low-dose (≤10 MBq) isotope (dye labelling is contraindicated in pregnancy).
- And after neoadjuvant systemic treatment, if regression, down-staging has occurred as a result of the treatment (cN positivity was turned to ycN0) (see "Neoadjuvant treatment" for details) (20).

Contraindication

- Inflammatory breast cancer.
- T4, tumours of stage 4.
- Lymph node metastasis confirmed by other methods [e.g., clinically/radiologically (PET CT) highly suspected axillary lymph node/s; ultrasound-guided FNA/core biopsy].
- Known allergic reaction to markers.

Axillary Lymph Node Dissection

During ALND, at least ten lymph nodes at axillary levels I and II should be removed, sometimes including also level III (5, 33–38). There are no clear international recommendations for the removal of lymph nodes at axillary level III, performable in cases of resectable Level III metastatic node/s, or in cN2 cathegory. Their removal does not significantly affect either disease-free or overall survival (20, 33).

If technically possible, branches of intercostobrachial nerve should be preserved, which results in reduced rate of postoperative pain and numbness in the upper limb (4).

Indication for Axillary Lymph Node Dissection

- concomitantly with surgical treatment of invasive breast cancer if preoperative clinical investigations (ultrasound-guided FNAC/core biopsy) have confirmed the presence of axillary lymph node metastases.
- After SLNB, if there is metastasis in >2 SLNs (macrometastases) and/or the patient does not meet selection criteria for study Z-0011 (38) [clinically negative (physical examination, AXUS, FNAC) axillary lymph nodes, breast-conserving surgery, up to two positive SLNs (micro/macrometastasis, macroscopic extracapsular tumour spread, lymph node conglomerate, neoadjuvant treatment), whole breast irradiation + adjuvant systemic treatment].

- Mastectomy and SLNB, if no postoperative radiotherapy is planned and the SLN (even if only one single lymph node) contains macrometastasis.
- If ultrasound-guided FNAC/core biopsy performed before neoadjuvant (primary systemic) treatment confirms lymph node metastasis and AXUS continues to report suspected lymph nodes after PST; concomitantly with breast surgery.
- Or if SLNB performed after neoadjuvant (primary systemic) treatment confirms axillary lymph node macrometastasis; concomitantly with or after breast surgery. In case of having only isolated tumour cells or micrometastases in the SLN/s after PST, the St Gallen Consensus Panel voted 89% and 60% against completional ALND (5).
- In cases of insufficient or no sentinel lymph node/s presentation (no hot spots), either pre- or intraoperatively; in such cases a so-called axillary lymph node sampling or limited axillary lymph node dissection (axillary sampling plus resection of any suspicios axillary lymph node/s) should carried out by removing at least four lymph nodes (up to 6 nodes) optimaly located at level I of the axilla. Criteria for this intervention are: invasive tumours confirmed by core biopsy; preoperative axillary ultrasound did not confirm suspect lymph nodes; and no nodules suspect of being enlarged metastases are observed during surgery. DCIS (no confirmed invasive/microinvasive parts), neither ALND nor sampling is required (33).

ALND Can Be Omitted

If clinically (AXUS negative, in cases of uncertainty AXUS-guided FNAC/core biopsy is negative) the result of disease assessment and SLNB (evidence 2.a) is cN0 (2–4, 20)

- pN0 (sn), i.e., no metastases in the sentinel lymph node(s).
- pN0 (i+) (sn), i.e., SLN involvement of ITC (isolated tumour cell) category can be confirmed.
- pN1mi (sn), i.e., SLN contains at most micrometastases.
- pN1a (sn), if only 1 to 2 SLNs are metastatic (macrometastases), the patient meets the inclusion criteria for study Z-0011 (38). If a clinically positive lymph node is confirmed at the time of diagnosis (US-guided FNAC/core biopsy has confirmed axillary lymph node metastasis) and regression, down-staging occurs as a result of primary systemic treatment, then the result of performed SLNB is ypN0 (sn), i.e., no metastases are present in the sentinel lymph node(s), and ALND may also be omitted. To reduce the rate of false negative results, at least three sentinel lymph nodes must be removed in such cases, and double labelling is mandatory, pretreatment metastaic lymph node marking is highly recommended. If fewer (1, 2) SLNs are removed, ALND can be replaced by axillary radiotherapy (36, 37).
- For mastectomy, if only 1–2 SLNs are metastatic, ALND can be replaced by axillary radiotherapy (7, 37).

Intraoperative Assessment of Sentinel Lymph Nodes

Indications for intraoperative assessment of SLNs and the resultant burdens for the patient (longer surgery time) and health care system have decreased significantly with the decreasing indications for ALND (36–40). Based on the new guidelines, and with increasing use of alternative axillary radiotherapy, ALND is indicated in an ever-smaller subgroup of patients (<10%).

Based on new indications for ALND, intraoperative SLN assessment is recommended in the following cases:

- When performing mastectomy, if adjuvant radiotherapy is not planned or not accepted by the patient in advance.
- During surgery following neoadjuvant/primary systemic treatment, if SLNB is performed, with a minimum requirement of removing at least two sentinel axillary lymph nodes for cN0 and three lymph nodes for cN1-ycN0.

SURGICAL TREATMENT OF NON-INVASIVE TUMOURS (CARCINOMA *IN SITU*)

In situ breast carcinomas include the more common and clinically more significant ductal carcinoma *in situ* (DCIS) and Paget's disease. The ductal form is now considered a precursor of invasive breast carcinoma. According to the new nomenclature, lobular carcinoma *in situ* (LCIS), which was previously classified into this group, is now called lobular neoplasia and, unlike DCIS, it is considered a non-obligatory precursor of invasive breast cancer, and not a malignant disease. It increases the risk of later breast cancer (RR: 5.4–12), but does not require active treatment. The pleomorphic and florid variant of LCIS may behave similarly to DCIS, so its treatment should be the same (41).

With the spread of populational mammography screening, the incidence of DCIS now exceeds 20% in some countries, compared with an earlier incidence of 1%. In untreated cases, the risk for progressing to invasive carcinoma within 10–20 years from the diagnosis is about 30–50%. Clinical observations suggest that the presence of a high-grade comedo-type DCIS and necrosis, as well as age less than 50 years, indicate poorer biological behaviour and also a higher likelihood of local recurrence. In practice, the so-called Van Nuys Prognostic Index and its improved version, the University of Southern California/Van Nuys Prognostic Index are useful tools. The latter also includes the completeness of surgical excision and the patient's age (the former did not take age into account) in addition to the size and pathological grade of the lesion, when calculating disease prognosis/recurrence. A separate category is the microinvasive (T1mi) form, which in terms of behaviour is closer to DCIS than to invasive cancers (42); the free 2 mm surgical margin that is adequate for a DCIS will therefore also be optimal here. In this case, a chance of metastasis is already present, but with a significantly lower frequency than in larger invasive tumours;

however, SLNB is required. The presence of a microinvasive focus is strongly correlated with the extent of DCIS.

Diagnosis

This disease is primarily detected on mammography screening in asymptomatic women in the form of calcifications of various sizes and appearances (sensitivity 87%–95%) (43). The increasing use of contrast enchanced MRI scanning may help determine the extent of the disease more accurately, especially in high-grade DCIS, where the sensitivity of the procedure is 73%–100% (43, 44), and this may also support the planning of accurate surgical treatment. This disease is associated with clinical symptoms, such as palpable lumps or nipple discharge, in only 5%–10% of the cases. The preoperative diagnosis with core biopsy (or vacuum-assisted core biopsy (VAB)) is essential, since this will clearly confirm the presence of the disease, and it is also suitable for the detection of possible invasive/microinvasive foci (necessitating axillary staging). If the non-malignant biopsy specimen does not contain calcification, sampling is generally not considered to be representative. In such cases, repeated image guided biopsy (optimaly VAB) should be done, if needed by insuffitient result of the repeated biopsy, image-guided (guided by wire, isotope labelling, radioactive or other magnetic labelling seeds) surgical excision for diagnostic purposes is warranted.

Surgical Treatment

There is no difference in survival between patients undergoing mastectomy and those undergoing breast-conserving surgery plus adjuvant whole breast irradiation.

Since in most cases the disease is not palpable, different kind of tumour labelling technique (wire hook or isotope labelling method, special seed markers) should be used in such cases to achieve successful surgical treatment (see below).

In case of breast conserving surgery, wide excision with a tumour free surgical margin is essential (26). For DCIS, due to a so-called discontinuous growth pattern, a broader intact safety zone is required, compared to invasive tumours. The NCCN (4) and the ESMO (3) consider that an intact margin of at least 2 mm is optimal. As the chance for local recurrence is higher for excisions with close margin/s (<2 mm), consideration of an additional treatment (re-excision, irradiation, tumour bed irradiation with an additional boost dose) is recommended. A close resection margin direct to the skin or to the chest wall continues to be an exception for re-excision, if the resection included the complete parenhcyma and superficial fascia till the subcutaneous fat and the pectoral fascia towards the posterior has also been removed (43). The presence of classical LCIS in the resection margin does not result in an increased local recurrence rate; in such cases, no additional excision or further surgery is required.

Mastectomy is primarily recommended (relative indication) for multicentric/diffuse and/or large (>50 mm) lesions. In cases when the mammary gland to tumour volume ratio (cosmetic result) is suboptimal one should consider surgical options of oncoplastic breast-conserving surgery or modern mastectomies plus immediate breast reconstruction. *In situ* ductal carcinoma can spread to the nipple via the central ductal branch, which is why SSM or ASM with nipple removal is recommended when choosing a type of modern mastectomy procedure and immediate reconstruction. If DCIS cannot be confirmed pathologically in tissue sample behind or direct from the nipple, NSM may also be performed (23). This surgery also provides a good opportunity for immediate breast reconstruction. There are no international first-level evidence recommendations for this indication (23). On pathological investigation, examination of the anterior resection surface is important.

Surgical Treatment of the Axilla in DCIS

DCIS is defined as non-invasive, which means that it cannot give rise even to lymph node metastases. However, there are reports in the world literature showing that lymph node metastases may occur in the sentinel lymph node in a low percentage of such cases (<10%) (see below). Based on the above, in selected cases, such as extensive tumour size (>50 mm), in the presence of histologically poorly differentiated comedo necrosis, or microinvasive foci, and if a mastectomy or removal of the axillary extension of the breast is planned, sentinel lymph node biopsy is recommended. In the latter cases, removal of the sentinel lymph node is necessary since if the final histological examination confirms invasive and/or microinvasive foci in the breast, SLNB will be significantly more difficult to perform or with less accuracy.

If preoperative investigations suggest pure DCIS less than 50 mm in size (confirmed on core biopsy), no sentinel lymph node biopsy is required in the same session with the excision. If the final histological befund confirms invasive/microinvasive foci in the specimen, SLNB is recommended in a second session.

Paget's Disease

Paget's disease is an *in situ* carcinoma localized within the skin of the nipple-areolar complex (NAC), with a possibility of having an invasive tumorfoci in the parenchyma in almost 80% of the cases. Further invasive or *in situ* foci without any clinicalor symptoms may often be detected accidentaly in peripherial areas of the breast pranehcyma by diagnostical imagines. Preoperative histological examination [surgical biopsy/full-thickness skin biopsy (punch biopsy)] is extremely important for an accurate diagnosis. Similarly, a complex breast imaging, including contrast enchanced breast MRI, is essential for the detection of occult ipsilateral or contralateral lesions. For *in situ* lesions only, the surgical treatment will be local excision with an appropriate tumour free margin and with complete removal of the nipple-areolar complex. If the presence of invasive carcinoma is confirmed, treatment is based on the principles applicable to solid tumours: excision of the central quadrant of the breast, inclusive of the NAC, or mastectomy (with SLNB or ALND; see below). If the invasive tumour is located peripherally, in addition to removal of the NAC, the tumour can be removed by oncoplastic techniques or via a separate skin incision with appropriate axillary staging.

If diagnostic core biopsy confirms other B3 lesions—atypical ductal hyperplasia (ADH), classical lobular neoplasia (LN) (45), flat epithelial atypia (FEA), papilloma (especially if larger than 10 mm, atypical, multiple, peripheral), radial scar, complex sclerosing lesion, phyllodes tumour (PT), atypical or rapidly

growing fibroadenoma or large or symptomatic pseudoangiomatous stromal hyperplasia—complete surgical removal is recommended. For B3 lesions (with the exception of ADH and PT), vacuum-assisted biopsy removal and close survaillance are also allowed if necessary technical conditions and experience are met (45).

Phyllodes Tumour and Sarcomas of the Breast

A tumour of fibroepithelial origin with benign, malignant and borderline forms. Core biopsy is essential for a diagnosis, and if this fails, an excisional biopsy is required, due to the heterogeneity of tumours. Core biopsy does not always result in an accurate diagnostic classification, therefore, cell-rich fibroepithelial lesions will represent category B3 and they should be removed *in toto* (see consensus recommendation on pathology).

Surgical Treatment

For a small phyllodes tumour (<5 cm), a wide excision in negative margins (1 cm macroscopic resection margin) without axillary staging will suffice, as this type of tumour may give rise to metastases via haematogenous but not lymphatic spread (except when the presence of axillary lymph node metastasis was confirmed preoperatively). Mastectomy is recommended for extensive lesions (>5 cm) and/or if oncological radicality is uncertain. If mastectomy is performed, immediate breast reconstruction can be carried out. For benign phyllodes tumours, a conservative approach is recommended; close surveillance seems to be sufficient for cases with possible microscopically positive margins, and is also allowed for borderline tumours, judged on individual basis, but in such cases adjuvant radiotherapy is required. For malignant phyllodes tumours, excision in negative margins and adjuvant radiotherapy if the breast is preserved are basic requirements.

In the event of local recurrence, further extensive excision or mastectomy is recommended.

Sarcomas of the breast are rare forming a heterogenous group of malignancies arising from mesenchymal tissues. There are approximately 4.6 new cases per million women per year and account for less than 1% of all breast malignancies (46). The primary sarcoma of the breast is associated with genetic conditions such as LiFraumeni syndrome, familial adenomatous polyposis, and neurofibromatosis type 1. Primary breast sarcomas are also associated with environmental risk factors like arsenic compounds, vinyl chloride, and alkylators. Secondary sarcoma of the breast most often occurs after breast irradiation or other former radiotherapy of intrathoracic malignancies such as nonHodgkin lymphoma. The most common sarcoma of the breast is secondary angiosarcoma. Angiosarcoma of the breast is associated with poor prognosis, and mastectomy is the mainstay of the treatment. In many advanced cases angiosarcoma seems to have a multifocal pattern. Therefore, wide peripheral surgical macroscopic margins of at least 3 cm are recommended.

Inflammatory Breast Cancer

This is a breast cancer with one of the worst biological behaviours. Its clinical appearance is explained by tumour invasion of the lymphatic vessels of the skin (breast swelling, marked oedema, erythema, peau d'orange), which mimics an inflammatory disease (T4d) (21).

Diagnosis is confirmed based on complex breast examination (US, mammography, MRI if necessary) and histological results (core, punch biopsy), but clinical diagnosis (lymphoedema and erythema involving more than 1/3 of the breast) is essential. At the time of diagnosis, lymph nodes are metastatically involved (N1–N3) in a significant proportion (approximately 80%), and distant metastases can also be detected in almost a quarter of cases. A thorough diagnostics for distant metastases is therefore recommended before starting therapy.

Its treatment primarily is not a surgical indication. Following effective neoadjuvant chemotherapy (and/or targeted therapy), modified radical mastectomy with a view to R0 resection is recommended (3, 4). Sentinel lymph node biopsy (SLNB) is contraindicated in inflammatory breast cancer due to a high false negative rate (of approximately 40%) (47); therefore ALND should be performed. Delayed breast reconstruction can be performed after a negative oncological control, and an appropriate tumour-free period (12 months).

Gestational Breast Cancer

Gestational breast cancer is breast cancer that occurs during pregnancy or afterwards during breastfeeding (within 12 months). Breast tumour is the most common oncological disease in pregnant women, with an incidence of 1:3000 (48). Diagnosis is usually late, so the prognosis is generally poor.

Treatment should be chosen according to the stage of the disease as in any other case. It should be noted, however, that radiation therapy is contraindicated during pregnancy, but chemotherapy can be administered relatively safely during the second and third trimesters (see Consensus on Systemic Treatment). Pregnancy is not a contraindication to surgery. For breast cancer detected in the first trimester, termination of pregnancy is not justified but should be discussed, and efforts should also be made to avoid preterm birth.

It is recommended that pregnant breast cancer patients are treated in specialy skilled care centres. Surgery can be performed in any trimester. The NCCN (4) recommends performing a mastectomy in the first trimester. In this respect, US and European recommendations differ somewhat (2–5). It should be emphasized that radiation therapy during pregnancy is contraindicated, but if radiation therapy can be postponed until after delivery, breast-conserving therapy does not present any disadvantages compared to mastectomy. However, in the first trimester, mastectomy is recommended due to the significant delay to radiation therapy. Proper axillary staging should be always a part of the surgical treatment. For a clinically negative axilla, sentinel lymph node biopsy may be performed. Use of low-dose isotope (≤10 MBq ^{99m}Tc), rapidly followed by surgery and excision of the injection site, after tracer administration, will pose a minimal risk to the fetus, so this can be safely performed during pregnancy as well as in early

breast cancer (49, 50). Administration of patent blue is contraindicated. Although large randomized trials cannot be expected due to the low number of cases, experience to date has shown that isotope labelling, with a low dose, can be considered a safe method. According to the St. Gallen recommendation, primary reconstruction with tissue expander after a modern mastectomy (SSM, NSM) is supported, though by a narrow majority; however, longer and more extensive surgery may result in more complications (2).

Breast cancer discovered during breastfeeding is treated according to its stage after cessation of breastfeeding.

Occult Breast Cancer With Axillary Lymph Node Metastasis

No malignancy/suspected malignancy can be confirmed in the breast with imaging studies (ultrasound, mammography, contrast enchanced MRI) and physical examination, but metastatic lymph node(s) is/are diagnosed in the armpit (by axillary ultrasound, lymph node core biopsy; the breast origin of the metastasis should be confirmed). Less than 0.5% of diagnosed cases are occult breast cancers. In each case, PET CT scanning is recommended to exclude other primary tumours.

Mastectomy (with or without reconstruction) with ALND is one of the available therapeutic options; another option is performing simple ALND followed by breast radiation therapy or other adjuvant oncology treatments. If no mastectomy is performed, some (20%–30%) of the tumours may later become radiologically detectable or symptomatic, and thus removable, therefore close surveillance is extremely important.

Breast Cancer in Young Women

In current literature, juvenile breast cancer is a term used for breast cancer under the age of 40. This age group does not fall into the age group for mammographic screening, therefore, in the majority of cases (90%) patients present with clinical symptoms. Statistics show that tumours with unfavourable clinicopathological characteristics and that are biologically more aggressive ("triple-negative," i.e., ER/PR and HER2-negative tumours) are more common below the age of 40. This is also supported by the fact that both recurrence-free and overall survival are lower in this age group (51). For juvenile breast cancer, there is always the possibility of familial, hereditary breast carcinoma. Based on the above, genetic consultation and screening of people carrying *BRCA1* and *BRCA2* mutations is recommended, in an accredited laboratory (2). Newly the St Gallen Consesnus Panel in 2021 stated, if a gene panel testing is chosen, the majority (67%) voted that the preferred panel should routinely include: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, STK11, RAD51C and RAD51D, and TP53 genes (5).

Locoregional and systemic treatment should always be individualized, and the principles of surgery do not change in juvenile breast cancer. As a treatment, mastectomy has no advantage over breast-conserving surgery plus radiation therapy in terms of either local recurrence or survival (52).

However, it is recommended that people carrying the mutation be informed in detail in a special centre about the advantages and disadvantages of treatment alternatives, while considering the specific psychosocial, sexual and body image aspects of the situation. The possibility and timing of breast reconstruction should also be addressed when informing the patient. There are several options for surgical treatment. For early breast cancer, breast-conserving surgery with complementary radiation therapy may be performed, if requirements are met. Another proposed alternative treatment is unilateral or bilateral mastectomy (even with immediate reconstruction), which reduces the chances of developing a second breast cancer and also increases disease-free and overall survival, in the long term (53, 54).

Male Breast Cancer

Its incidence is quite low (male/female ratio 1/100–200), accounting for about 0.2% of malignancies in men. This can be an explanation for the fact that these cancers are detected in a localy advanced stage in most of the cases, and therefore their prognosis is less favourable. Tumour size at the time of discovery is similar to that of female breast cancers, but due to the lack of mammary parenchyma, involvement of the skin and nipple-areola is more common. Diagnostic procedures and staging are the same as for female breast cancers. All men diagnosed with BC should be referred for genetic counselling and, if indicated, *BRCA* mutation testing.

Treatment is also the same as for female breast cancers. From a surgical point of view, the typical central location of the tumour and the low breast tissue to tumour ratio should always be considered. In operable patients, mastectomy and SLNB or ALND when lymph nodes are involved should be the procedures of choice (3, 55). Unlike the volume replacement and aesthetic reconstruction of the female breast, in male cases, it is the primary skin replacement that may represent a challenge for reconstructive surgery.

Risk-Reducing Mastectomy

Prophylactic bilateral breast removal and breast reconstruction are warranted in high-risk women (carrying certain gene mutations, or who had prior breast irradiation due to lymphoma).

According to the St Gallen Consensus Statement in 2021 the Expert Panel favored consideration of risk-reducing mastectomy for women harboring highly penetrant genes (e.g., BRCA1, BRCA2, TP53, and PALB2), and surveillance with mammography and magnetic resonance imaging (MRI), for women with intermediate penetrance genes (e.g., BARD1, CHEK2, CDH1, and STK11). For women with less penetrant gene mutations (such as ATM, BRIP1, NF1, RAD51C, and RAD51D), the Panel strongly favored surveillance without prophylactic mastectomy (5).

Contralateral risk-reducing mastectomy in patients with breast cancer who carry a genetic mutation may be warranted (evidence 3.b). Up to the age of 80 years, the mean cumulative breast cancer risk of patient carrying *BRCA* mutations is 83% (±7%) for *BRCA1* and 76% (±13%) for *BRCA2*; however, its main feature of this form of the disease is onset at a young age

(<40 years) (56). By merely performing bilateral prophylactic mastectomy, the incidence and mortality of breast carcinoma can be reduced by 90%–95% (evidence 3.b) (3, 57).

Gene testing can only be performed in accordance with strict professional standards in accredited laboratories. *BRCA1/2* mutation carriers or other mutations holders with high penetrant genes (see above) should also be informed and various therapeutic options (such as close follow-up, oncopsychological guidance, lifestyle counselling, family screening, reproductive counselling, chemoprevention, and prophylactic mastectomy) should be discussed only in specialized centres with adequate knowledge and experience (21). During genetic testing, *BRCA* mutations are most commonly examined; however, if these are not present and if there is significant family history, other less common genetic disorders should also be considered (Li-Fraumeni syndrome: *p53* mutation; Cowden's syndrome: *PTEN* mutation; *ATM* mutation; Lynch-syndrome: *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PMS2* mutation, *RAD51* mutation, *BRIP1* mutation, *PALB2* mutation, *CHEK2* mutation, Peutz-Jeghers syndrome: *STK11* mutation, *CDH1* mutation).

During prophylactic mastectomy, simple mastectomies, SSM, ASM, NSM (evidence 3.c) may be performed as necessary, depending on the patient's parameters, breast size, and other plastic surgical considerations, with immediate or delayed-immediate breast reconstruction, using biological or synthetic meshes, with expander or silicone implant (evidence 5.c). These surgeries require thorough multidisciplinary preparation, in view of the high-risk group of patients.

Routine sentinel lymph node removal during purely prophylactic surgery is not justified; the chance of occult disease is <5%.

In the United States (58) and to a lesser extent in Europe (57), increasing numbers of women with breast cancer prefer mastectomy, and also request contralateral risk-reducing breast removal. Beneficial effects of bilateral mastectomy on survival if the genetic test is negative have not yet been demonstrated (59, 60, 61). In such cases, careful patient information is also required (2, 3).

BREAST RECONSTRUCTION

In a significant proportion of breast cancer patients, complete breast removal is still required for proper oncological surgical care (11, 21, 23, 62). Breast reconstruction is also provided for female patients who have undergone mastectomy. In accordance with European recommendations, when performing mastectomy, the patient must be informed in writing and verbally before surgery about the possibility of breast reconstruction. Indications or contraindications for reconstructive surgery are assessed, and the optimal time for surgery is determined at the mandatory preoperative multidisciplinary breast oncology team meeting (with a plastic surgeon as a member) together with the patient. When reconstruction is requested, the complex treatment plan (in the absence of other contraindications) should take into account the reconstructive surgery, requiring cooperation between the surgeon performing the oncological surgery and the plastic surgeon performing the reconstructive surgery, unless it is performed by a single oncoplastic breast surgeon trained in both areas and with appropriate professional experience. Post-mastectomy breast reconstruction surgery using autologeous flaps may be performed by a plastic surgeon, where minimum professional standards for the procedure are met. Post-mastectomy reconstructive surgery can be performed within one session with tumour removal (immediate reconstruction) or in a delayed version. If oncological treatment has been sufficiently radical to allow immediate/delayed-immediate or two-stage breast reconstruction, SSM, ASM, NSM or SRNSM mastectomy using a state-of-the-art surgical technique is recommended. Oncological results of the latter mastectomies (only those performed with a state-of-the-art surgical technique) are comparable to those of traditional mastectomies. These were professionally endorsed by the St. Gallen Consensus Conference in 2013 (11). Such skin-sparing mastectomies require special expertise and professional experience, and incomplete implementation of these methods results in a significant oncological risk and under-treatment. Skin-sparing mastectomies should only be performed if there is an immediate or delayed-immediate breast reconstruction plan.

Breast reconstruction is a relative indication for surgery, but it is an essential component of the oncological management of breast cancer. It aims to improve quality of life, by acting as one of the most important physical and mental rehabilitation interventions. Breast reconstruction does not delay adjuvant treatment nor affects the treatment outcome, including survival or local control and doesn't hinder follow-ups. The choice of optimal breast reconstruction technique is the responsibility of the plastic surgeon/oncoplastic breast surgeon, and should be made according to circumstances of the case and the patient's preferences.

The choice of the optimal breast reconstruction method depends on:

- Patient body type (breast size, obesity).
- Comorbidities (e.g., diabetes) and habits (smoking).
- The type of mastectomy and skin incision (skin-sparing, nipple-sparing).
- The quantity and quality of remaining tissue.
- The plan of multimodal treatment (postoperative radiation therapy or chemotherapy).
- The patient's mental and physical performance status.
- Surgeon' Experience.

Depending on when it is performed, breast reconstruction may be:

- Immediate, when reconstruction or some reconstructive steps are performed at the same time of the mastectomy.
- Delayed-immediate, when after SSM,ASM, NSMg, a tissue expander is placed sub- or epipectoral, to bypass the period of adjuvant multidisciplinary treatments, after which

reconstruction is completed at a delayed time point using silicone breast implants or autologous flaps.
- Delayed, when one- or multiple-step of breast reconstruction is performed (several months/years) after tumour removal and adjuvant treatment, if there is negative staging.

In recent years, with the broader use of skin-sparing mastectomies, immediate and delayed-immediate breast reconstructions have gained priority, as they have significant cosmetic, psychological, and economic benefits compared to delayed reconstructions.

Immediate or delayed breast reconstruction options after mastectomy:

- Breast reconstruction with autologoustissues:
  - With (vascular pedicled or free) flaps transplanted from the abdominal wall or back area (e.g. transverse rectus abdominis (TRAM) or deep inferior epigastric perforator (DIEP) flaps) or the dorsum (latissimus dorsi flap (LD) flap etc.).
  - With local flaps.
- Breast reconstruction with implantation of a tissue expander, especially if adjuvant radiotherapy is planed or had been performed (delayed immediate, or two stage reconstructions) followed by the replacement of definitive silicone implant.
- Breast reconstruction with a silicone implant and a special biological or synthetic mesh (direct to implant techniques) that reinforces the lower pole of the breast (e.g., acellular dermal matrix or various synthetic meshes placed partially subpectoral or prepectoral). The meshes or matrices are crucial in prepecotoral implant-based breast reconstructions (63).
- Breast reconstruction with the combination of autologous tissue (flap) and implant or tissue expander (hybrid reconstructions).
- In cases when post-mastectomy radiation therapy (PMRT) has to be given, the rate of complication of immediate breast reconstructions is increased (capsular contracture, fibrotic transformation of the autologous flap, etc.) If PMRT is given, delayed-immediate (using tissue expander) or delayed breast reconstruction is recommended. The implant placement phase of a delayed-immediate reconstruction or a delayed reconstruction is recommended after complete tissue consolidation or at least 6 months after radiation therapy.
- In case of autologous tissue reconstruction and radiation therapy, the aesthetic outcome of breast reconstruction surgery may be worse than expected, but clinical data are conflicting.
- If a tissue expander or an implant is placed followed by radiation therapy, the rate of early and late complications are significantly higher (capsular contracture, seroma, trophic ulcer).

According to the St Gallen Consensus Statement 2021 with respect to the timing and sequence of reconstruction and postmastectomy radiotherapy, the Expert Panel was completely split about the optimal strategy: delayed reconstruction after radiotherapy 20%, immediate implant in 1 or 2-stage 23%, immediate autologous reconstruction 25%, delayed immediate (expander) 32%—with a large number of abstentions, indicating that there is no established standard with respect to this issue (5).

When tissue reaction (redness, epidermolysis, oedema, etc.) ceases following radiation therapy, possible radiodamaged tissues (e.g., capsular contracure) should be resectedcompletely, or the use of autolgous fat transplantation can promote tissue revascularisation and regeneration. The best functional and aesthetic outcome could be achieved by autologous breast reconstruction. Loss of breast skin can be replaced by local and distal flaps, while the parenchymal volume of the breast can be replaced by implants or autologous flaps. Trends of the last decade have been heading towards implant-based immediate/delayed-immediate reconstructions, since these are with less surgical burden on the patient, the morbidity of the flap donor areais prevented and the patient's own tissues can be retained for any subsequent salvage interventions.

In patients under age 40 with a cancer family history, genetic testing (BRCA1/2) should be considered before surgery.

When planning a delayed reconstruction, the need for genetic testing should always be considered.

PRIMARY SYSTEMIC (NEOADJUVANT) TREATMENT

A known benefit of primary systemic oncology treatment (PST) is that primarily unresectable tumours may become resectable if they respond well to PST, thereby increasing the rate of breast-conserving surgeries (64, 65, 66). Results reported so far suggest that its effect on disease-free (DFS) and overall survival (OS) is equivalent to that of adjuvant systemic treatment, provided that it is followed by curative surgery and oncology treatment (65). There is also evidence that using neoadjuvant treatment in primary operable cases has no survival advantage over adjuvant treatment, but a minimal increase in the number of locoregional recurrences (evidence 2.a) has been demonstrated (67); it is extremely important to bear this in mind when considering neoadjuvant treatment (6).

Neoadjuvant treatment may be required in patients with stage IIA, IIB, T3N1M0 cancers, where breast-conserving surgery cannot be performed due to unfavourable tumour to breast volume ratio and/or when the patient refuses mastectomy. There is a growing evidence to support the fact that among stage II tumours, primary systemic treatment is worthwhile first of all for ER/PR, HER2-negative (triple-negative) and HER2-positive tumours, when tumour size is larger than 2 cm and/or axillary metastases are present, as well as for ER-positive postmenopausal tumours, where the rate of pathological remission ("down-staging/sizing") is significantly higher (2–4).

Additional criteria for surgical treatment:

- Core biopsy from the primary tumour and tumour centre labelling (with marker clips/markers).
- FNAC/core biopsy is required in all cases in which axillary lymph node metastasis is suspected clinically and/or on ultrasound scanning.
- Clip marking of the metastatic lymph node is recommended for cases with limited axillary metastatic lymph nodes, in cases in which there is a real chance of cN1− ycN0 (see above TAD).
- MRI scanning is required for treatment monitoring and for designing the final surgical plan, to accurately assess the size and location of the residual tumour (the issue of preserving nipple-areolar complex).
- Indication for neoadjuvant treatment, treatment monitoring and recommendation for subsequent surgical/ oncological treatment can only be determined on an individual basis, by the multidisciplinary onco- team.

The choice of the final surgical treatment will depend on the effectiveness of PST, which can be evaluated using complex breast assessment (ideally contrast-enhanced breast MRI) performed before and after systemic treatment. If partial or complete tumour regression is achieved, breast-conserving surgery can be performed often with techniques used to remove non-palpable tumours. Further conditions enabling breast-conserving surgery are as follows: the tumour can be removed with microscopical free surgical margins; no extensive microcalcification suspicios for malignancy demonstrated on mammogram; and an adequate cosmetic result can be achieved with the breast conserving surgery. Surgical excision of the tumour is performed based on the tumour size remaining after the PST, using a marker clip/ marker inserted before treatment (2, 67).

For tumours with aggressive biological behaviour (e.g., triple negative, HER 2 positive, grade III, high Ki67) the volume of the breast tissue to be removed should be considered carefully on an individual basis, and the specimen should be large enough to allow an accurate pathological analysis, regardless of the degree of regression (67). Intraoperative specimen radiography/ mammographic of the oriented specimen is a prerequisite. Tumour bed should be marked with clips. During surgery, effort should be made to completely remove the microcalcification. There are also data showing that in selected cases, breast-conserving surgery can also be carried out for multifocal and multicentric tumours, if surgical excisions can be performed with a microscopical free surgical margins (2, 68).

Treatment of the Axilla/Sentinel Lymph Node Biopsy

An axillary SLNB may be performed before initiating primary systemic therapy. Advantages of the method: it provides a more accurate stage assessment; ALND does not need to be performed later, in the event of a negative SLN; and irradiation of the lymphatic region is also not needed. The disadvantage is that the patient undergoes additional surgery before treatment (which means an increased burden on the patient, along with non-negligible costs); in the event of a positive SLN, ALND must be performed even after PST, if the treatment leads to ycN0 status. In half of the cases, this means over-treatment, since as a result of PST, the axillary lymph node metastasis may regress completely (down-staging), and often only the SLN is positive, but other axillary lymph nodes are not. Benefits of SLN biopsy after neoadjuvant treatment: the patient undergoes one single surgery and ALND can be avoided in a significant number of cases, and it also provides an opportunity to evaluate the axillary response to oncology treatment. The disadvantages of this method are that identification rate of the biopsy is lower, while the rate of false negative cases as well as of axillary recurrences is higher. However, based on the results of several prospective randomized studies, reliability of SLNB after neoadjuvant treatment may be enhanced if a double labelling method (isotope + dye) is used and if at least 3 SLNs are removed (69–72). Based on the above and in line with international recommendations, SLNB is the preferred method for assessing axillary status after neoadjuvant treatment (2, 4, 73, 74). The treatment of the axilla in connection with neoadjuvant therapy is summarized below (**Table 1**). (See above TAD and metastatic lymph node marking before PST)

Recommended Treatment

For clinically/ultrasound-positive axilla:

- ALND is required, if the core biopsy/aspiration cytology of the suspected lymph node is positive and if, after neoadjuvant treatment, the lymph node is still positive clinically and/or based on core/aspiration test.
- If the core biopsy/aspiration cytology of the suspected lymph node is negative, a SLNB should be considered prior to PST; if the result is positive, ALND should be performed after PST.
- If the core biopsy/aspiration cytology of the suspected lymph node is negative and no SLNB is performed before PST, it can be performed (with double labelling only) after successful PST (axilla is also clinically negative during surgery); in the event of a pathologically positive SLNB, ALND should be performed in one session (see above new St Gallen Statement in cases of isolated tumor cells and micrometastases).
- If the axilla is clinically positive (cN1) (negative core biopsy/ cytology of the suspected lymph node) and becomes clinically negative following neoadjuvant systemic treatment, removal of three or more sentinel lymph nodes is allowed instead of immediate ALND. If all sentinel lymph nodes removed are negative, no additional axillary surgery is required. If less than 3 (1, 2) SLNs were removed, and these were found to be pathologically negative, axillary radiotherapy should be considered (69).
- If the core biopsy/aspiration cytology of the suspected lymph node is positive and ultrasound-guided labeling of the lymph node is possible before neoadjuvant treatment, and the labeled lymph node can be removed after treatment by targeted axillary surgery (TAD), and it is histologically negative together with 1 or 2 additional SLNs,

TABLE 1 | Surgical treatment of the axilla after neoadjuvant therapy (7, 33).

Baseline Lymph node status	Lymph node status after neoadjuvant therapy	Axillary surgery	Results of Lymph node pathology examination	Complementary axillary intervention	Regional Lymph node irradiation
cN0	ycN0	SLNB	ypN0	No	No
			ypN1	ALND	Yes, if adverse factors*
cN1	ycN0	SLNB* or TLNB (TAD)	ypN0	No	Yes, if adverse factors*
			ypN1	ALND	Yes
cN1	ycN1	ALND	ypN0	No	Yes, if adverse factors*
			ypN1	No	Yes

SLNB: sentinel lymph node biopsy, SLNB: double labelling, removal of at least 3 SLNs, TLNB: targeted lymph node biopsy (Selective removal of metastatic lymph node(s) marked before neoadjuvant therapy), TAD: targeted axillary dissection (combination of TLNB ans SLNB), ALND: axillary lymph node dissection, AxRT: axillary radiation therapy. *Adverse factors: age <40 years, Grade: 3, triple-negative breast cancer, T3 T4, low tumour regression grade (TRG).*
For pN2 pN3, ALND and AxRT are recommended

complementary ALND may be omitted in certain cases (see above targeted axillary approaches) (37, 73, 74).
- In patients with baseline cN2 axillary positivity, ALND with regional irradiation should be performed after treatment, regardless of the response to neoadjuvant treatment.

For clinically / ultrasound-negative axilla:

SLNB can be performed both before and after neoadjuvant systemic treatment (after neoadjuvant systemic treatment double labeling, removal of at least 3 SLNs). If fewer than 3 SLNs were removed during SLNB after PST and if these are found to be negative on pathology examination, axillary irradiation should be considered, due to a higher false negative rate.

In case of cN0 before PST, if sentinel lymph node (SLN) cannot be identified after PST either by preoperative lymphoscintigraphy or using intraoperative techniques (dye labelling and/or isotope labelling), four node sampling technique or TAD could be done to prevent overtreatment. In case of macrometastatic lymph node ALND is recommended (see as well ST Gallen 2021 by ypN0 (i+) and ypN1 (mi) (72).

In cases that cannot be classified according to the above suggestions, the multidisciplinary onco-team should decide on the adequate treatment on an individual basis.

PALLIATIVE SURGICAL TREATMENT OF BREAST CANCER

The treatment of advanced breast cancers is complex and involves all disciplines of a multidisciplinary expert team (pharmacology, radiotherapy, and surgical oncology, diagnostic imaging, pathology, gynaecology, psycho-oncology, social work and palliative care) (78, 79). From the very first moment of diagnosis, the patient should be provided with appropriate psychosocial support and supportive treatment, and adequate interventions should be performed according to their symptoms. Actual palliative interventions should be decided individually at a multidisciplinary onco-team meeting level.

Currently, palliative surgical removal of the primary tumour in *de novo* stage IV breast cancers cannot prolong survival, with the exception of cases with bone-only metastases (79, 80). E2108, a randomized trial of surgery in women with *de novo* stage IV breast cancer, showed that breast sugery does not improve overall survival, thereby contradicting the results of multiple observational studies, while prior randomized trials have provided conflicting data (81). According to BOMET MF 14-01 study, timing of primary breast surgery either at diagnosis or after systemic therapy provided a survival benefit similar to ST alone in *de novo* stage IV BOM BC patients. This is the followup study to their randomized trial (82).

Surgery may be considered in selected patients to improve quality of life, but the patient's opinion should always be taken into account. If surgery is performed, it should aim at radical removal of the primary tumour. In selected cases, where oligometastatic disease and/or low-volume distant metastasis is sensitive to systemic treatments and complete regression occurs, making long-term survival a reality, locoregional curative treatment should be considered.

Several earlier studies suggested that mBC patients may benefit from surgical removal of the primary cancer. Three randomized trials, among them Austrian Breast and Colorectal Cancer Study Group trial 28, however, yielded conflicting results with a Turkish study suggesting a potential benefit of surgery (83).

In ECOG-ACRIN 2108 with mBC without disease progression after 4–8 months of systemic therapy were randomized to continued systemic therapy with or without additional early local therapy (81). The majority of patients had luminal/HER2-negative breast cancer, 37.9% presented with bone-only disease and 53.8% had received upfront chemotherapy. In the overall study population, no difference in terms of OS was observed (HR 1.09; 95% CI 0.80–1.49); in the subset of patients with mTNBC, additional ELT seemed to have a detrimental effect (risk for death HR 3.5; 95% CI 1.16–10.57). Therefore, additional locoregional therapy may not be regarded as a standard component of mBC treatment.

Prospective clinical trials are needed to more accurately assess the oncological value of locoregional treatments for stage IV breast cancers.

Surgery is indicated when prevention and treatment of bleeding, ulceration or infection is targeted, or for hygienic reasons. If mastectomy is required to achieve radical locoregional control, plastic surgery reconstruction may be needed.

SURGICAL TREATMENT OF LOCOREGIONAL RECURRENCES

Recurrence After Breast-Conserving Surgery

The rate of recurrence after previous breast-conserving surgery and subsequent radiation therapy is less than 5%, due to multimodal treatment (75). In the event of a recurrence in the breast or a new primary tumour, mastectomy (after having former WBRT) is usually recommended. Depending on the viability of the skin and the time elapsed since irradiation, immediate reconstruction is also possible for cases with R0 resection. Furthermore, particularly good (cosmetic and oncological) results have been published recently with modern skin-sparing mastectomies (75). However, it has also been shown that, under special conditions, repeated breast-conserving surgery may also be justified. According to the St Gallen Consensus Statement 2021 a major change occurred for ipsilateral local recurrence, because the majority of the panel endorsed another breast conservation procedure with radiotherapy, if the lead team is more than 5 years (Expert Panel 63%) (5). Factors that would favour a second breast conservation were defined as: low risk (small, luminal A; 81%); intermediate (5-year) interval since first diagnosis (64%); the panel was split 50: 50 on how the issue should be handled in patients for whom re-irradiation is not an option (5).

The most important criteria for this choice are:

- Tumour smaller than 2 cm.
- Solitary lesion.
- Radiation therapy can be repeated with acceptable toxicity (this may be brachytherapy or, if primary APERT has been performed, total breast irradiation may be carried out).
- If explicitly requested by the patient, after adequate information (higher recurrence rate can be expected) (75).

In cases of recurrences developing after mastectomy, a wide excision is recommended (complemented by radiation therapy, if this was not performed previously), if the foci are radical resectable (R0 excision). It may often be necessary to involve a plastic surgeon to achieve proper soft tissue coverage (flaps) of the chest wall.

Treatment of the axilla in cases of breast cancer recurrence (76):

- If SLNB or limited axillary dissection (fewer than ten lymph nodes have been removed) was previously performed and the patient is currently cN0 staged, reSLNB (ALND for positive SLN) or ALND is recommended. In case of or cN+ ALND is the treatment of choice.
- If ALND was carried out previously (more than ten lymph nodes removed) and the axilla is currently clinically negative, axillary surgery is not recommended; however, if it is clinically positive, axillary exploration and removal of the remaining lymph nodes is necessary.
- Contralateral SLNB is recommended if lymphoscintigraphy clearly indicates the presence of sentinel lymph nodes or a hot spot.

Treatment of isolated axillary recurrence:

- ALND after SLNB (with surgical exploration of interpectoral area and of level III).
- Axillary exploration after ALND, removal of recurrent tumour (when R0 resection is possible).

In the case of supra- or infraclavicular recurrence, systemic treatment and radiation therapy are preferred (77).

SURGICAL TREATMENT OF DISTANT BREAST CANCER METASTASES

Breast cancer with distant metastases or stage IV is a treatable disease, but it is currently considered incurable, with a median overall survival of 3 years and a 5-year survival of 25% (74, 78, 79). Significant improvements in metastatic breast cancer survival have been achieved in recent years.

However, since distant metastases are local manifestations of a systemic disease, removal of the metastasis alone is not sufficient if the above results are to be achieved; this must be part of a multimodal treatment. Additionally, local surgical treatment should only be considered in cases of oligometastases, which means the presence of solitary or up to five metastases, not necessarily in the same organ.

Metastasectomy/radiation therapy, should be based on a multidisciplinary onco- team decision, is most likely to be considered in the following cases:

- Young patient in good general health condition.
- Small tumour volume.
- Long disease-free period.
- Free from local tumour recurrence.
- Feasibility of R0 resection (80).
- Tumour molecular subtype.

Even for unresectable metastases, histological sampling from the metastasis (surgical/non-surgical biopsy) should be sought, since changes in the primary tumour and the receptor status of metastases, as well as the exclusion or identification of a second, unknown primary tumour, may be crucial in the treatment of metastases (81).

Treatment of Metastases by Organs

Liver

Liver metastases of breast cancer are associated with a higher risk of mortality than involvement of any other distant organ (lung, bone, brain). 5-year survival is 3.8–12% (median survival: 4–21 months) (83, 84, 85).

Currently, no high-level evidence for the oncological effectiveness of surgical removal of liver metastases is available. Local treatment of isolated liver metastases may

improve survival only in well-selected cases. Patient selection should be performed from a biological perspective by a multidisciplinary onco-team, for well-assessed, histologically confirmed metastases, taking into account tumour molecular subtype (best ER-, HER2-positive tumour), biological behaviour (disease-free interval between the onset of the primary tumour and of the metastasis should be as long as possible), good tumour response to systemic treatments; metastasectomy should be R0; good general condition, burden of surgery as low as possible (laparoscopy, tumour ablation) and low complication rate are important, so that any further postoperative systemic treatment (evidence 5.c) is not delayed.

Lungs

The general principles also apply to the resection of lung metastases, but DFS and OS increases in only a small proportion of patients. It is recommended that metastasectomy be carried out via a minimally invasive video thoracoscopic procedure (VATS) (evidence 5.c).

Malignant Pleural Involvement

Requires systemic treatment; if confirmed involvement would change the oncological treatment plan, thoracocentesis and cytological analysis of the aspiratum should be considered, although the false negative rate is high (evidence 3.b). Drainage is only recommended in symptomatic cases with clinically significant amount of hydrothorax (evidence 3.a). Insertion of an intrapleural drain or administration of talc and drugs (bleomycin, biological response modifiers) may be helpful (evidence 3.b).

Bone

The most common sites of bone metastases are the femur, vertebrae, upper arm, collarbone, and jawbone. Surgery should be considered if there are fractures or an extremely high risk of fracture, which is most often followed by radiation therapy. Pathological fractures of the femur are the most common, followed by pathological fractures of vertebrae and spinal stabilization surgeries due to their risk (evidence 1.a). Neurological symptoms indicative of spinal cord compression are an emergency, warranting neurosurgical or orthopaedic decompression surgery following diagnostic imaging (MRI). If this is not possible, emergency radiation therapy is required (82). Surgical interventions are complemented by targeted radiation therapy and systemic treatment. If there is no risk of pathological fracture, radiation therapy is recommended (evidence 1.a).

Brain

10%–30% of patients with metastatic breast cancer will have a brain metastasis, and solitary cerebral metastasis will occur in 10%–20% of patients. According to randomized clinical trials, neurosurgery/metastasectomy or stereotactic radiosurgery is recommended for this group (evidence 1.b). With complementary whole -brain radiation therapy, this reduces the risk of local and complete cerebral recurrence and increases overall survival (evidence 1.c). Surgical or radiosurgical treatment of solitary or multiple brain metastases is recommended, while for unresectable metastases, the latter is considered.

ISSUES RELATING TO COOPERATION BETWEEN SURGEONS AND PATHOLOGISTS

Storage of Surgical Preparations (Before Delivery to the Pathology Department)

It is advisable to make the surgical preparation available to the pathology department/pathologist immediately after removal (within a maximum of 30–60 min), without formalin fixation and any incision, and to store it at 4°C until delivery. This may also enable tissue bank sampling. If this is not possible, to ensure optimal receptor assessment, it is advisable to start fixation of the fresh preparation in 10% formalin a minimum of five times the volume of the tissue, preferably stored at 4°C (in a refrigerator), and to store samples in a refrigerator at 4°C until delivered to the pathology department. A validated alternative is vacuum packaging and storage at 4°C followed by transport. In addition to tissue structure, these methods provide the best preservation of both receptor proteins and nucleic acids for optimal assessment of predictive biological markers.

Specimen Orientation

The surgical specimen should be labelled in the operating room, clearly specifying at least three poles, e.g., medial, lateral and superior. Separate marking of the specimen located just behind the nipple is also required in cases of a nipple-sparing mastectomy. The details of orientation should also be recorded by the pathologist in the description.

If intraoperative histological examination of the retroareolar surface or retro/intermammillary specimen is required, the clinical question should be discussed in advance with the pathologist.

The pathologist should be notified if a previously marked (sentinel) lymph node is also removed after neoadjuvant treatment; the presence of a clip in the lymph node, confirmed on intraoperative specimen radiography/mammography and pathological examination, should be recorded in the surgical description so that all previously marked (marked) lymph nodes were removed during SLNB (72, 73).

Radiological Examination of the Specimen

For tumours that are non-palpable or not clearly palpable, specimen mammography or ultrasound is required to facilitate pathological processing, irrespective of whether breast-conserving surgery or mastectomy is performed. In cases of a neoadjuvant treatment a clip should be placed into the tumour bed in foreward if clinical complete regression is a realistic option, except in cases when extensive microcalcification is remaining after treatment. The resected specimen should also be sent for intraoperative specimen radiography/mammography or ultrasound scanning to confirm removal of the tumour, and

also in order that the pathologist be able to find the tumour bed and judge the exact tumour size.

NEW SENTINEL LYMPH NODE BIOPSY METHODS

Over the past years, several alternative methods have been introduced for sentinel lymph node biopsy. Of these, ICG (indocyanine green) fluorescent labelling, among many clinical applications, may also be used to identify axillary sentinel lymph nodes and perform biopsy (86). Studies to date have shown that the rate of sentinel lymph node identification and sensitivity of the method do not differ significantly from radiolabelling, and these values are better when these methods are used in combination. However, obesity and older age will reduce the identification rate (87).

Magnetic marking of the sentinel lymph node with nanocolloid containing iron oxide (superparamagnetic iron oxide (SPIO) may also be used (87). The detection rate of SLNs and sensitivity of the method are equivalent to those of the radioisotope method. Combined application of these methods may improve sensitivity. However, the magnetic carrier enters the liver and spleen and is stored there, which may make subsequent MRI scanning difficult. This procedure cannot be used when metal implants are located close to the region of interest.

Based on the most recent meta-analysis, both methods, when used alone, show better results than blue dye labelling alone and are equivalent to the classic dual, isotope, and blue dye combination (88–90). In institutes where isotope labelling is not possible, the alternative methods presented here are indeed applicable, but, naturally, after proper validation.

This is part 2 of a series of 6 publications on the first Central-Eastern European Professional Consensus Statements on Breast Cancer covering imaging diagnosis and screening (91), pathological diagnosis (92), surgical treatment (present paper), systemic treatment (93), radiotherapy (94) of the disease and related follow-up, rehabilitation and psycho-oncological issues (95).

AUTHOR'S NOTE

The consensus document contains product placement without the intention of advertising. Each complex molecular test is unique, and although these can be described without indicating their name (for example with the number of genes tested), not everyone will necessarily understand what this refers to. For this reason, and adopting the practice used in some of the source works, the tests are listed under their trade name.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.por-journal.com/articles/10.3389/pore.2022.1610377/full#supplementary-material

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Radiotherapy of Breast Cancer—Professional Guideline 1st Central-Eastern European Professional Consensus Statement on Breast Cancer

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The international radiotherapy (RT) expert panel has revised and updated the RT guidelines that were accepted in 2020 at the 4th Hungarian Breast Cancer Consensus Conference, based on new scientific evidence. Radiotherapy after breast-conserving surgery (BCS) is indicated in ductal carcinoma *in situ* (stage 0), as RT decreases the risk of local recurrence (LR) by 50–60%. In early stage (stage I-II) invasive breast cancer RT remains a standard treatment following BCS. However, in elderly (≥70 years) patients with stage I, hormone receptor-positive tumour, hormonal therapy without RT can be considered. Hypofractionated whole breast irradiation (WBI) and for selected cases accelerated partial breast irradiation are validated treatment alternatives to conventional WBI administered for 5 weeks. Following mastectomy, RT significantly decreases the risk of LR and improves overall survival of patients who have 1 to 3 or ≥4 positive axillary lymph nodes. In selected cases of patients with 1 to 2 positive sentinel lymph nodes axillary dissection can be substituted with axillary RT. After neoadjuvant systemic treatment (NST) followed by BCS, WBI is mandatory, while after NST followed by mastectomy, locoregional RT should be given in cases of initial stage III–IV and ypN1 axillary status.

Keywords: breast cancer, radiotherapy, guidelines, radiation oncology, consensus

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INTRODUCTION

Radiation therapy (RT) remains an essential part of complex breast cancer therapy that according to recent treatment trends are based on both the risk status and use of individualized RT technique chosen also considering the input from the patient. Results published in the past 3 years since the 3rd Breast Cancer Consensus Conference did not bring about fundamental changes in the clinical practice of radiation therapy, but modification and updating the radiation therapy guidelines is

necessary based on new scientific evidence. RT after breast-conserving surgery (BCS) is indicated in ductal carcinoma *in situ* (stage 0), since it decreases the risk of local recurrence (LR) by 50–60% (1–9). In early stage (stage I-II) invasive breast cancer RT remains a standard treatment following BCS; however, in elderly (≥70 years) patients with stage I, hormone receptor-positive tumour, the alternative treatment choice of hormonal therapy without RT can be considered (10–17). Hypofractionated (15 × 2.67 Gy) whole breast irradiation (WBI) is a validated alternative that is equivalent to the conventional five-week (25 × 2 Gy) WBI (18–23). In selected cases, RT of the entire breast is not required following BCS, and RT of the tumour bed and surrounding tissues (so-called accelerated partial breast irradiation; APBI) can be used as a substitute (24–36). Following mastectomy, RT significantly decreases the risk of LR and improves overall survival of patients who have 1 to 3 (pN1a) or ≥4 (pN2a, pN3a) positive axillary lymph nodes (37–45). For patients with positive lymph nodes, evidence from a randomized clinical trial supports radical mastectomy followed by hypofractionated RT of the chest wall, axillary apex, and supraclavicular region (21). There is no high-level evidence for the hypofractionated treatment of parasternal lymph nodes. According to the latest randomized trials (EORTC 22922/10925 and NCIC-CTG MA.20), regional RT significantly improves both disease-free and distant metastasis-free survival, while its effects on overall survival are contradictory (46–47). Based on the latest surgical studies, in selected cases with one to two positive sentinel lymph nodes there is no need for complementary axillary dissection. But with the exception of micrometastases (pN1mi) irradiation of axillary lymph nodes or—depending on individual risk—lymph nodes in other nodal regions it is recommended (48–52). In all indications (DCIS, invasive breast cancer and regional irradiation) intensive research is in progress to predict the benefit of RT using various molecular markers with the aim of deescalating therapy in low-risk cases that do not require RT (53).

After neoadjuvant systemic treatment (NST) followed by BCS, WBI is mandatory, while after NST followed by mastectomy, postoperative RT should be given in cases of initial stage III–IV and ≥ypN1 axillary status (54–65). For a great majority of patients, RT is based on high-level evidence. In the future, clinical validation of molecular and genetic markers can provide better personalized RT. The following RT recommendation categories are based on the levels of evidence supporting treatment guidelines and agreement between members of the expert panel:

Evidence levels:

1. Meta-analysis of randomized trials
2. Randomized trials
3. Prospective trial, retrospective studies
4. Expert opinions

Recommendation categories:

1: Full consensus, level 1 evidence
2a: Full consensus, level 2–3 evidence
2b: Generally broad consensus, level 2–3 evidence
3: No consensus, level 2–4, equivocal study results, or few or complete lack of empirical evidence.

RADIATION THERAPY PRINCIPLES—TECHNICAL CRITERIA FOR IRRADIATION, TARGET VOLUMES, AND DOSING

The entire treatment plan must be reviewed before beginning RT. The patient must be informed of the benefits and expected adverse reactions of RT. RT is contraindicated during pregnancy.

The use of three-dimensional conformal RT (3D-CRT) or other up-to-date modalities (IMRT, VMAT, or brachytherapy) are recommended to achieve control of the doses irradiated to the target volumes and the surrounding healthy tissues. Internationally recognized limit values are available for the description of dose coverage and—especially in the case of hypofractionated RT—dose homogeneity as well as the doses received by healthy tissues [heart, LAD, lungs, contralateral breast, or in the case of accelerated partial breast irradiation (APBI) the ipsilateral breast, and in some cases the cervical vessels or brachial plexus].

Healthy organs are protected in multiple ways, for example, when treating the left side, the heart may be protected by deep inspiration and breath-holding as well as individual positioning (prone versus supine). In certain cases the dose received by organs at risk can only be kept at acceptable levels by dose optimisation with inverse treatment planning.

Whole Breast Irradiation

Target volumes: The whole residual breast. "Boost" treatments delivered with brachytherapy use clinical target volume (CTV) specifying the area corresponding to the original tumour with a 2 cm safety zone (RT safety zone = 20 mm—intact surgical margin in mm) (recommendation category: 2b) (66). Hence, in brachytherapy, no additional PTV-CTV expansion is necessary (PTV=CTV). In teletherapy, the recommendation is to extend the CTV by an additional 0.5 cm when using fractionated image-guided RT and an additional 1 cm when performed without image guidance; the latter is to compensate for the greater inaccuracy of the settings and displacement due to respiration (PTV) (28). The size of PTV-CTV extension requires individual consideration depending on the patient fixation and QA protocols used in each centre. If the surgical margin cannot be defined in each direction, then "boost" irradiation is to be performed to the tumour bed plus a 15 mm extension (CTV) (recommendation category: 3).

Technical criteria for optimal radiation therapy: Megavoltage irradiation (4–10 MV photon), CT-based three-dimensional conformal radiation therapy (3D-CRT), and use of tangential fields. The exposure of the lungs and the heart must be minimised (recommendation category: 1) (67–71), which in a certain proportion of cases will require the use of special irradiation techniques (irradiation during deep inspiration and breath-holding or respiratory gating, intensity-modulated RT—IMRT, or RT with the patient in prone position) (70–79). Simple control

measurements include the central lung distance (<3 cm) and the maximal heart distance (<1 cm), and a more accurate method is the analysis of the dose-volume histogram (DVH). In order to achieve homogeneous dose distribution, the target volume can be divided into subfields (segments) or compensators and wedge fields can be used, while IMRT is recommended for large breasts (recommendation category: 2a) (80). Additional ("boost") dose can be directed to the tumour bed with an accelerator (electron, photon) or with brachytherapy (usually interstitial needle implant). For small breasts and more superficial tumours, electron beam irradiation is usually preferable; for large breasts and deeply situated tumours brachytherapy or 3D conformal photon "boost" is recommended. When using "boost" treatment, the tumour bed must be intra-operatively marked with titanium clips to avoid the geographical miss of the target volume (67, 81–83). For oncoplastic procedures, appropriate documentation and communication about the surgery are important.

Ideally, RT should start after wound healing, the recommended period is 4–6 weeks—but no more than 12 weeks—after the surgery (recommendation category: 2a). Following adjuvant chemotherapy, RT is started after a 3-week off-treatment period after the last chemotherapy cycle (recommendation category: 2b). Accelerated partial breast irradiation (APBI) may also be administered prior to the adjuvant chemotherapy (15). Percutaneous "boost" treatment is performed after whole breast irradiation and without a break—as long as no radiation dermatitis of more than grade 2 is present (recommendation category: 2b). In case of serious (grade 3) dermatitis a 1–3 week-long off-irradiation period can be considered. While brachytherapy "boost" treatment is usually performed 1–3 weeks after the completion of whole breast irradiation, it can also be performed as a perioperative brachytherapy "boost" therapy before the whole breast irradiation (recommendation category: 3). Percutaneous "boost" therapy can be combined with IMRT as a simultaneous integrated "boost" treatment (SIB) (recommendation category: 2b).

Dosing: The basic dose schedule is 40–42.5 Gy (2.67 Gy/fraction, 5 times a week, in 15–16 fractions) or 45–50.4 Gy (1.8–2 Gy/fraction, 5 times a week, in 25–28 fractions) (recommendation category: 2a). Dose usually refers to that given to the isocentre. Accelerated hypofractionated treatment requires paying close attention to the dose limits of organs at risks (heart and lungs) and to dose homogeneity, which provides local tumour-free results identical to standard fractionation and the fractionation schemes are also at least equivalent in terms of adverse reactions (18–23). Based on the 5-year results of the FAST-FORWARD trial extreme hypofractionation (e.g., 5 fractions of 5.2 Gy on 5 consecutive days) is a promising treatment option. However, longer follow-up and further prospective trial data are needed before its implementation into the routine daily practice. Extremely hypofractionated WBI should be considered only in the context of prospective clinical trials. Additional ("boost") dose of the tumour bed is performed with external RT of 10–16 Gy (2 Gy/fraction, 5 times a week), or with high dose rate (HDR) brachytherapy 1 × 10 Gy or 3×4–5 Gy. SIB IMRT includes 50 Gy (2 Gy/fraction, 5 times a week) irradiation to the whole breast and 60 Gy (2.4 Gy/fraction, 5 times a week) to the "boost" target volume, or using hypofractionated treatment with 21 × 2.17 Gy to the whole breast +21 × 2.66 Gy to the "boost" target volume (total doses received by the whole breast and tumour bed are 45.6 Gy and 55.9 Gy, respectively), but many other variations of fractionation can be used.

Accelerated Partial Breast Irradiation

Target volume: Determination of target volume is based on tumour bed markers (clips) (67, 84). In the absence of tumour bed markers, US or CT can be used to determine the target volume (recommendation category: 2b). In the absence of clips, partial breast irradiation is only feasible if the tumour bed is clearly visible and identifiable using imaging methods ("cavity visibility score"; CVS≥3) (85). The clinical target volume (CTV) for brachytherapy is the area corresponding to the original tumour with a 2 cm safety zone (RT safety zone = 20 mm—intact surgical margin in mm) (recommendation category: 2b) (67). In brachytherapy, no additional PTV-CTV expansion is necessary (PTV=CTV). In teletherapy, the recommendation is to extend the CTV by an additional 0.5 cm when using fractionated image-guided RT and an additional 1 cm when performed without image guidance; the latter is to compensate for the greater inaccuracy of the settings and displacement due to respiration (28). The size of PTV-CTV extension requires individual consideration, depending on the patient fixation and QA protocols used in each centre. When administering partial breast irradiation with teletherapy, fractionated image guidance is recommended to decrease target volume extension and to minimize adverse reactions (recommendation category: 2b).

Technical criteria for optimal radiation therapy: APBI can be administered via interstitial brachytherapy, 3D-CRT or IMRT (24–31, 33–36, 86). Partial breast irradiation using a single high-dose (1×20–21 Gy) intraoperative electron beam therapy or low energy (50 kV) X-ray therapy significantly increases the risk of local recurrence and therefore cannot be recommended for routine care (recommendation category: 2a) (87, 88). Accelerated hypofractionated treatment requires paying close attention to the dose limits of organs at risk (heart and lungs).

Ideally, RT should start after wound healing, and the recommended period is 4–6 weeks—but no more than 12 weeks—after the surgery (recommendation category: 2a). After adjuvant chemotherapy, RT is started at the end of a 3 weeks off-treatment period after the last chemotherapy cycle, but due to its short treatment period (4–5 days) accelerated RT can also be administered before chemotherapy without the risk of a significant delay in systemic treatment (recommendation category: 2b).

Dosing: Fractionated HDR or ultrafractionated PDR afterloading technique. Using PDR brachytherapy, the dose is 45–50 Gy, and the dose rate is <1 Gy/hour. Fractionated HDR brachytherapy of 7 × 4.3 Gy, 8 × 4 Gy, or 10 × 3.4 Gy, two daily treatments (leaving at least 6 h between the fractions) (29, 30, 32–34). At present APBI with extreme hypofractionation (1–4 treatment fractions, in 1–2 days) can only be administered in

prospective clinical studies (25, 26, 35). Appropriate dose homogeneity (dose homogeneity index; DHI>0.65) and at least 90% coverage of target volume (coverage index; CI ≥ 0.9), maximum skin dose <70%. Using 3D-CRT or IMRT the dose is 9 × 4.1 Gy or 10 × 3.85 Gy, with two daily treatments (27, 28, 34, 36), or 5 × 6 Gy or 15 × 2.67 Gy, with one daily treatment (24). Dose prescription for ICRU point (isocentre; 100%). PTV coverage: $V95_{PTV}$=100% (PTV is covered by the 95% isodose surface).

Chest Wall Irradiation

Target volume: Operated chest wall area with surgical scar and lobe, and if possible, the site of the surgical drain.

Technical criteria of optimal radiation therapy: Use of up-to-date megavoltage machine (high-energy photon or electron beam), CT-based RT planning, at least 3D-CRT recommended to provide maximum protection for the heart and lungs. Use of tangential photon or direct electron field(s). In order to achieve even dose distribution, subfields (segments), compensators (wedge filters), or bolus or IMRT can be used.

Ideally, RT should start after wound healing, and the recommended period is 4–6 weeks—but not more than 12 weeks—after the surgery (recommendation category: 2a). When administering adjuvant chemotherapy, RT is started after a 3 week off-treatment period following the last chemotherapy cycle (recommendation category: 2b).

Dosing: The standard dose schedule is 40–42.5 Gy (2.66–2.67 Gy/fraction, 5 times a week) or 45–50.4 Gy (1.8–2 Gy/fraction, 5 times a week). In the START studies (START-A, B, and Pilot) less than 10% of the patients (513 patients out of 5,861) were treated with mastectomy (23). The 5-year results of the Chinese post-mastectomy randomized study were published in 2019 (21). The rates of locoregional results and complications were similar with hypofractionation (15 × 2.9 Gy) and conventional fractionation (25 × 2 Gy). The parasternal lymph nodes were not irradiated (recommendation category: 2a) (19–23). Extremely hypofractionated WBI should be considered only in the context of prospective clinical trials. Accelerated hypofractionated treatment requires paying close attention to the dose limits of organs at risk (heart and lungs) and dose homogeneity. If there is a positive or close (<2 mm) surgical margin a "boost" dose applied to the surgical scar is 10–16 Gy (2 Gy/fraction, 5 times a week) (89).

Irradiation of the Lymphatic Regions

The definition of the target volume depends on the type of axillary surgery (sentinel lymph node biopsy or axillary dissection) and the pathology status of the axillary lymph nodes. When performing sentinel lymph node biopsy, it is recommended that a surgical clip be placed at the site of the excised lymph node (recommendation category: 2b). This marker can assist in the assessment of dose coverage in various field layouts and irradiation techniques (66). When the patient is in a supine position during RT, the exposure of the lymphatic regions from tangential fields is inadequate (90), and the use of fitted additional fields has not been widely used due to the uncertainty originating from repositioning.

Levels 1–3 of the axilla for the contouring of the medial supraclavicular and parasternal lymph node regions must follow the anatomical borders (90–94). According to the newest European recommendations, exposure of the cervical vessels must be avoided during irradiation of the medial supraclavicular region (93).

Target Volumes

- Level I of the axilla
- Level II of the axilla (frequently treated together with the interpectoral/Rotter lymph nodes)
- Level III of the axilla
- Medial supraclavicular region (also called level IV of the axilla)
- Parasternal/internal mammary region

Conventional Field Layouts

- Elective supraclavicular field: supraclavicular and infraclavicular region + axillary apex (levels III–IV)
- Supraclavicular-axillary field: supraclavicular and infraclavicular region + axilla (levels I–IV or levels II–IV)
- Parasternal field: ipsilateral parasternal area including at least the first three intercostal spaces.

Technical Criteria of Optimal Radiation Therapy

- Supraclavicular-axillary region: Megavoltage irradiation (4–10 MV photon) with 3D conformal RT planning. During concurrent irradiation to the nodal region and the residual breast or the chest wall, the use of a single isocentre or the IMRT technique produce the best dose distribution.
- Parasternal region: The position of the parasternal lymph nodes (target volume: ipsilateral intercostal spaces 1–4) is indicated by the course of the internal mammary artery. Use of deep tangential fields should be avoided since the exposure of the critical organs (heart and lungs) is significant under such circumstances. Use of 3D-CRT or IMRT is essential to decrease the radiation exposure of the heart and lungs, and in some cases compromising the dose administered to the parasternal lymph nodes (46–48 Gy) may be necessary.
- Dosing: 40 Gy (2.67 Gy/fraction, 5 times a week) or 45–50.4 Gy (1.8–2 Gy/fraction, 5 times a week) (recommendation category: 2a) (18–23). Hypofractionation is still controversial when used for the irradiation of the internal mammary chain of lymph nodes, and some experts recommend conventional fractionation (recommendation category: 3).

Radiation Therapy of the Locoregionally Advanced Breast Cancer

Target volumes: Breast or chest wall, all unilateral lymphatic regions, and for "boost" treatments the tumour or tumour bed +1.5–2 cm safety zone.

Technical criteria of optimal radiation therapy: see the previous three chapters.

Dosing: The standard dose for target volumes is 50 Gy (2 Gy/fraction, 5 times a week), since in most cases the internal mammary chain is part of the target volume (recommendation category: 2b). Hypofractionated application of the dose (40–42.5 Gy in 15 fractions) in locoregionally advanced breast cancer is not supported by high-level evidence, but it can be used, based on positive experiences in prospective studies following breast-conserving surgery (recommendation category: 3). Additional ("boost") irradiation of 10–26 Gy is recommended for residual tumours.

RADIATION THERAPY TREATMENT GUIDELINES

In situ Breast Cancer (Stage 0, pTis N0 M0)

Lobular Carcinoma *In situ*

RT is not necessary (recommendation category: 2a).

Ductal Carcinoma *In situ*

- Irradiation is usually recommended after breast-conserving surgery, because 50 Gy administered to the residual breast decreases the risk of local recurrence by 50%–60% in all risk groups (recommendation category: 1) (1–9). Usually, 50% of local relapses are DCIS and the other 50% are invasive cancer. For low-risk patients (well-differentiated lesion, with minimal or no necrosis, at least 10 mm safety zone, >60 years of age) radiation therapy may be omitted based on individual assessment (recommendation category: 3). The significance of "boost" dose is still unclear. For young (≤45 years of age) patients (recommendation category: 2a) or high-grade DCIS or narrow surgical margin (<2 mm) (recommendation category: 3) a boost dose should be considered (8, 95). Partial breast irradiation for DCIS can only be administered in the framework of a prospective clinical trial (recommendation category: 3) (31).
- Chest wall RT is not required after mastectomy (recommendation category: 2A).
- Irradiation of lymphatic regions is not justified: pTis N0 M0 (recommendation category: 2A).
- In cases of Paget's disease of the nipple, wide cone excision should be followed by RT of the residual breast (recommendation category: 1).

"Early Stage" Invasive Breast Cancer: Stage I–II, T1-2 N0-1 M0, T3 N0 M0

Partial Mastectomy Followed by Irradiation of the Residual Breast Tissue

Contraindications of breast-conserving surgery (in cases of DCIS and of invasive cancer):

- Prior RT of the breast or chest wall
- Pregnancy—if the postoperative RT would be administered during the pregnancy
- Diffuse microcalcification (suggestive of malignancy)
- Positive surgical margin after reexcision
- Connective tissue disease: scleroderma, lupus (relative contraindication)
- Patient is germline TP53- and ATM-mutation carrier
- Premenopause with known BRCA1-2 mutation (relative contraindication), due to a high risk of local recurrence (second primary tumour). Breast-conserving surgery requires prior discussion with the patient with detailed description of future risk of cancer.

- Irradiation of the residual breast decreases the risk of local recurrence by 75% in all age groups (recommendation category: 1) (10, 11, 14–17). RT also significantly improves the 15-year breast cancer-specific survival—by 5% and 7% in patients with negative or positive lymph nodes, respectively (10). Accelerated hypofractionated whole breast irradiation (15 × 2.67 Gy or 16 × 2.66 Gy) is an equivalent alternative to conventional fractionation (50 Gy/5 weeks), provides local tumour-free results identical to standard fractionation and does not increase the incidence or severity of late adverse reactions (recommendation category: 1) (18–23). Based on the first results from the FAST-Forward randomized study, whole breast irradiation of 5 × 5.2 Gy administered over 1 week is effective, and at the 5-year follow-up point does not increase the rate of late adverse reactions. However, taking into consideration the scarcity of experience and lack of long-term follow-up results, its use outside of the clinical study setting is currently not recommended (recommendation category: 3) (96). In young patients whole breast RT may be used after chemotherapy and with concurrent regional RT and "boost" irradiation (recommendation category: 2b) (18–21, 23). For older (≥70 years of age) patients with good prognosis (stage I, negative surgical margin, hormone receptor-positive tumour) discontinuing RT and using only endocrine therapy can be considered—with the informed consent of the patient—since RT does not improve 10-year overall survival, but the patient must be fully informed of the significantly higher risk of local recurrence (at 10 years the rate is 10% without RT and 2% with RT) and its consequences (recommendation category: 2a) (12, 13).
- Treatment of the tumour bed with elevated ("boost") dose improves local tumour control in all risk groups, but for low-risk patients the absolute benefit of this treatment is limited (≤3% at 20-year follow-up) (recommendation category: 1) (15, 81–83, 97, 98).

Indications of an Additional ("Boost") Dose

Absolute indication (the presence of just one of the conditions is sufficient) (recommendation category: 1):

- Microscopically positive surgical margin (in the absence of reexcision)
- Small surgical margin (intact surgical margin <2 mm)
- ≤50 years of age
- Triple-negative breast cancer
- Poorly-differentiated (grade 3) tumour

Relative indication (recommendation category: 2A):

- Extensive intraductal component (EIC)
- Lymphovascular invasion
- Mitotic activity index (MAI) > 10 (/10 NNL)
- pT ≥ 3 cm

- Accelerated partial breast irradiation (APBI) is the standard treatment alternative to whole breast irradiation in selected low-risk cases (32). When adjuvant chemotherapy is indicated, APBI may be administered either before chemotherapy or after the completion of chemotherapy (15). Using interstitial brachytherapy with appropriate technique or external RT (3D-CRT or image-guided IMRT) the local tumour-free results are non-inferior compared to those achieved with whole breast irradiation, and the rate of late adverse reactions is not higher (recommendation category: 2a) (24, 27–34). For patients who prefer APBI with 3D-CRT or IMRT, once daily fractionation (15 × 2.67 Gy over 3 weeks) should be chosen (24), or if twice-daily fractionation (9 × 4.1 Gy or 10 × 3.85 Gy) is preferred then the patient should be informed of the potential benefits and risks of external RT as well as of the fact that contradictory results have been published regarding the cosmetic results and late adverse reactions of APBI with twice-daily fractionation (28, 34, 36, 86) (recommendation category: 2B). When using twice-daily fractionation, the target volume should be kept below 160 cm^3 (28, 34) (recommendation category: 2b).

Indications of APBI

Low-risk patients who are eligible for APBI outside of the framework of a clinical trial (recommendation category: 2a) (31):

- >50 years of age and
- Unicentric/unifocal invasive carcinoma and
- pT1-2 (≤30 mm) tumour size and
- Negative surgical margin and
- pN0 axillary status (with sentinel lymph node biopsy or axillary dissection) and
- EIC-negative tumour and
- Absence of lymphovascular invasion

Note: All criteria must be simultaneously met.

Moderate-risk patients are only eligible for APBI in the framework of a prospective clinical trial or after obtaining informed consent. If APBI is used outside of a clinical trial, the patient must be informed about the paucity of long-term results and what that means in terms of potential risks (recommendation category: 3) (31):

- >40–50 years of age or
- Unicentric, but multifocal tumour (within 2 cm of the primary tumour) or
- Pure DCIS or
- pN1mi (micrometastasis)

Note: The presence of only one criterion is sufficient to meet the moderate-risk status.

High-risk patients for whom APBI is contraindicated (recommendation category: 1) (31):

- ≤40 years of age
- pT2 (>30 mm), pT3, pT4 tumour size
- Positive surgical margin
- Multicentric or multifocal tumour (spreading beyond 2 cm of the primary tumour)
- EIC-positive tumour
- Positive for lymphovascular invasion
- pNx (unknown) or pN1a-2a-3a [1 or more macroscopic (>2 mm) positive lymph node] axillary status
- Breast-conserving surgery after prior neoadjuvant chemotherapy

Note: The presence of only one of the criteria is sufficient to meet this risk category.

Chest Wall Irradiation After Mastectomy

- pT1-2 pN0-1mi: Irradiation is not needed if the tumour was resected with intact surgical margins (recommendation category: 1). Although chest wall irradiation slightly decreases the rate of local recurrence at 5 years (from 1.9% to 1.2%), it does not improve breast cancer-specific survival (37). According to the NCCN protocol, chest wall irradiation should be considered if the intact surgical margin is ≤ 1 mm (15).
- pT3 pN0: Chest wall irradiation is recommended (recommendation category: 2a) (38).
- pT1-2 pN1a-2a-3a: Locoregional RT is recommended (recommendation category: 1).
- RT decreases the incidence of local recurrences at 5 years by ~15% (1–3 positive lymph nodes: from 17% to 3%, 4 or more positive lymph nodes: from 26% to 11%) and improves 20-year breast cancer-specific survival by 8–10% (37).
- pT1-2 pNx or pN0 but <6 examined lymph nodes (except when sentinel lymph node biopsy was performed): irradiation should be considered (recommendation category: 2b).
- Immediate breast reconstruction following mastectomy: the reconstructed breast and the chest wall are treated according to the above guidelines. The two-stage procedure provides a better result than immediate reconstruction with implant: expander insertion, irradiation of the expander, and after the irradiation the expander is replaced with the permanent implant.

Sentinel Lymph Node Biopsy Followed by Irradiation of the Axillary-Supraclavicular Region

- pN0-1mi (sn): If the sentinel node (SN) is negative or if there is a micrometastasis, usually there is no need for nodal irradiation (recommendation category: 2a), but irradiation of axilla levels 1–2 should be considered if there is an increased risk (histology indicated an aggressive tumour,

>pT1, multifocality, presence of LVI, a single SN was removed, systemic therapy is anticipated to have low or no efficacy, young age of the patient) (recommendation category: 3).

- pN1a (sn): If there is a macrometastasis (>2 mm) in the sentinel lymph node and axillary dissection is performed, then RT of the supraclavicular region (level 4) and axillary apex (level 3) is recommended, while there is no need to irradiate levels 1–2 (recommendation category: 2a). If no axillary dissection is performed (according to ACOSOG Z011 criteria), then irradiation of the axillary lymph nodes and, based on individual risk, other regional lymph nodes is required, since an incidence of metastases of 27–38% is estimated in the non-dissected non-sentinel lymph nodes (recommendation category: 2b) (48, 50, 99). Generally, levels 1–4 of the axilla are irradiated (recommendation category: 2a), but in the presence of lower risk it is sufficient to irradiate levels 1–2 of the axilla (favourable histology, pT1, unifocality, only one of several sentinel lymph nodes is involved, size of macrometastasis is <7 mm, effective systemic therapy, relatively older patient; recommendation category: 3). The RT performed instead of axillary dissection is equivalent to surgery in terms of nodal relapse-free results and overall survival (recommendation category: 1) (51, 52).

Axillary Lymphadenectomy Followed by Irradiation of the Axillary-Supraclavicular Region

- pN0-1mi: RT is not necessary (recommendation category: 1).
- pN1a, 2a, 3a, pN3c (ipsilateral sub-/supraclavicular lymph node metastasis): RT of the supraclavicular region and axillary apex is recommended (recommendation category: 2a) (46, 47, 100). If there has been adequate axillary dissection (≥6 removed lymph nodes) the use of elective supraclavicular field is sufficient, while irradiation of levels 1–2 is not required (recommendation category: 2a).
- pNx or pN0 but <6 examined lymph nodes (except when sentinel lymph node biopsy was performed): After inadequate lymphadenectomy (<6 processed lymph nodes) RT of the supraclavicular and axillary region (levels 2–3) is recommended based on individual consideration, but in general the targeted irradiation of axillary level 1 is not required (recommendation category: 2b).

RT of Lymph Nodes Along the Internal Mammary Artery

- pN0-1mi: Irradiation is not necessary (recommendation category: 2a).
- pN1a, pN2a, pN3a: If there are four or more positive axillary lymph nodes, RT of the parasternal region is recommended; if there are 1–3 positive lymph nodes, the decision to use RT is to be based on the individual consideration of the organs at risk doses and on the benefit gained represented by the risk of parasternal lymph node metastasis (recommendation category: 2b) (46, 100, 101). The value of elective irradiation of parasternal lymph nodes has not been elucidated completely, and radiation therapy professionals should always consider the risks of lung and heart exposure. Clinical manifestation of parasternal lymph node recurrence is very rare (<1%) and according to the latest published studies the role of parasternal lymph node irradiation in improving overall survival is not fully clarified, hence the routine elective RT of this region is still controversial (recommendation category: 3) (46, 100, 101).
- pN1b, pN1c, pN2b, pN3b: If there is histologically confirmed internal mammary sentinel lymph node or clinically unequivocal (CT, UH, MRI) parasternal lymph node metastasis, irradiation is recommended even in the presence of negative axillary status (recommendation category: 2a).

Radiation Therapy After Neoadjuvant Systemic Therapy

The efficacy of individualized neoadjuvant systemic therapies continues to improve, as shown by the improvement in pCR rates. A good response indicates a lowered risk of locoregional relapse, and in some cases RT can be avoided. A key consideration is that neoadjuvant systemic therapy can reduce the need for radical RT, which is one of its anticipated benefits compared to the adjuvant scheme.

Radiation Therapy After Neoadjuvant Systemic Therapy and Breast-Conserving Surgery

RT of the residual breast is recommended in all cases (recommendation category: 1) (54, 55, 64). After administration of the 50 Gy standard dose, a 10–16 Gy tumour bed "boost" should be considered (recommendation category: 3). The use of moderately hypofractionated regimens (e.g., 15 × 2.67 Gy or 16 × 2.66 Gy) for whole-breast irradiation are also acceptable. Administration of this additional dose should be based on the usual risk factors (age, histological type, initial grade, multifocality, surgical margin, lymph node status, and the detection of vessel invasion). In the NSABP B-18 and B-27 trials, the rate of local recurrence among patients receiving breast-conserving surgery and breast-only irradiation was around 10% (64). The predictors of local recurrence are the following: lack of pCR (especially ypN positivity), young age (<50 years), and advanced initial stage. In a similar patient group treated at the MD Anderson Cancer Center, in addition to advanced initial grade the following factors proved to be predictors of local recurrence: cancer of grade 3, and hormone receptor-negativity, presence of lymphovascular invasion, multifocal residual carcinoma, and close surgical margin (54, 56).

Chest Wall Irradiation After Neoadjuvant Systemic Therapy and Mastectomy

Clinical stage II: If there is a negative surgical margin (and ypN0 axillary status) RT is not required (recommendation category: 2b) (54, 55, 57–63, 65). If there is a positive surgical margin 50 Gy chest wall irradiation +10 Gy boost (2 Gy/day) irradiation is recommended and should be administered in all cases in

TABLE 1 | Recommendation for regional irradiation after neoadjuvant systemic therapy.

Initial status	Status after neoadjuvant treatment	Surgical (pathology) status	RT indication
cN0	cN0	ypN0 (sn)	No RT
cN0	cN0	ypN1 (sn)	ABD ± RT or RT
cN1 (f), pN1 (sn)	cN0-1	ypN0	No RT
cN1, pN1 (sn)	cN1	ypN1-2–3	RT
cN2 (f)	cN0	ypN0	RT or OBS

which irradiation of the lymphatic regions is necessary (recommendation category: 2a).

Clinical stage III–IV: In case of negative surgical margin (and ypN0 axillary status) 50 Gy chest wall irradiation, in case of positive surgical margin 50 Gy chest wall irradiation +10 Gy boost (2 Gy/day) irradiation is generally recommended and should be administered in all cases in which irradiation of the lymphatic regions is necessary (recommendation category: 2a) (54, 55, 57–63, 65). With the improving efficacy of systemic treatments, we can anticipate that pCR cases with no need of RT will become increasingly common, provided that the initial stage of the tumour is not advanced. Mastitis carcinomatosa cases require a wide (≥10 mm) safety margin during RT.

Irradiation of the Lymphatic Regions

At present, recommendations for optimal surgical and RT care following neoadjuvant systemic therapy are still based on retrospective data (101, 102). According to the Sentina clinical study, 70% of sentinel lymph node-positive cases become sentinel lymph node-negative in response to neoadjuvant chemotherapy, and in such cases regional irradiation can be omitted. At the same time, data published on the use of old diagnostic and therapeutic options suggest that regional irradiation is expected to have significant benefit in cases with initially advanced tumor stage and/or lymph node status (cN2-3) (53–55). A recent publication based on the analysis of a large database has highlighted the significance of the pathological tumor response in predicting the benefit of regional irradiation (102). Accordingly, in cases with initially positive lymph node status achieving ypN0 in response to neoadjuvant therapy, the benefit of irradiation is primarily associated with the histological type (hormone receptor-negativity) rather than the initial lymph node status. In such cases the indication of regional irradiation should be determined on an individual basis. The results of the first randomized trial (NSABPB-51/RTOG 1304) on regional irradiation used in cases with cN1→ypN0 are expected to be published in 2020 (103-108).

Table 1 shows the recommendations on regional irradiation following neoadjuvant systemic therapy (recommendation category: 2b) (54, 55, 57–63, 65).

Radiation Therapy After Breast Reconstruction

Reconstruction With Silicone Implant

Irradiation can be administered with no significant change in dosing. Nevertheless, an elevated risk of capsular contracture must be considered. Good cosmetic results can be achieved with careful fractionation and moderate dose (45–50.4 Gy, 1.8 Gy/fraction), and eschewing a bolus or additional dose (recommendation category: 2b) (109, 110). Hypofractionated treatment schedules are not recommended in the case of silicone implants, but in case of implanting a temporary expander by a two-stage reconstruction procedure, hypofractionated doses may be given.

Reconstruction With Autologous Tissue

RT does not significantly compromise the cosmetic results. The restrictions regarding silicone implants do not apply here (recommendation category: 2b) (109, 110). Use of hypofractionated treatment schedules is not recommended.

Irradiation and Systemic Treatment

- RT is administered after chemotherapy (recommendation category: 2b), but should be completed within 7 months after surgery (111, 112).
- There is no need to suspend trastuzumab therapy during irradiation (recommendation category: 2b) (111, 113).
- Aromatase inhibitors can be administered concurrently with RT (recommendation category: 2b) (111, 112, 114). Concurrent administration of tamoxifen and RT may increase the rate of grade 1 lung and breast fibrosis, but since its clinical relevance is not proven, concurrent administration can be considered on an individual basis (recommendation category: 3) (111, 112, 114, 115).

Radiation Therapy for Rare Diseases

Occult Breast Cancer (T0 N1-2 M0)

Occult breast cancer (axillary lymph node metastasis without identified primary tumour) requires the removal of axillary lymph nodes. Usually systemic therapy precedes RT (15).

Mastectomy is followed by irradiation of the axillary-supraclavicular region; in the case of breast-conserving surgery both the breast and the axillary-supraclavicular region require irradiation (recommendation category: 2b) (116). The dose is 50 Gy, and an additional 10 Gy "boost" can be applied in the presence of extensive axillary metastasis. Hypofractionated application of the standard dose (40–42.5 Gy in 15 fractions) in occult breast cancer is not supported by high-level evidence, but it can be used based on positive experiences in prospective studies following breast-conserving surgery (recommendation category: 3).

Malignant Phyllodes Tumours

Malignant phyllodes tumours are characterized by fast local expansion and high rates of local recurrence. The incidence of axillary metastasis is low (1.5%). The literature data are contradictory with respect to the value of postoperative RT. RT generally decreases the risk of local recurrence, but does not improve tumour-specific survival (117) (recommendation category: 2b). Irradiation with 50 Gy dose is recommended after mastectomy and positive or unclear surgical margin, or for the treatment of residual breast after excision. After breast-conserving surgery, following the standard dose of whole breast irradiation, a dose of 10–16 Gy "boost" should be considered (recommendation category: 3) (117). Borderline tumours require individual consideration.

Primary Breast Sarcomas

After breast-conserving surgery, doses of up to 50 Gy are recommended for the residual breast and 60–66 Gy to the tumour bed (recommendation category: 2b) (118). In the case of carcinosarcoma—with positive axillary lymph nodes—RT of the lymphatic regions is also recommended.

Secondary Sarcoma (Angiosarcoma) in the Conserved Breast

After mastectomy, reirradiation with hyperfractionated RT on an individual basis can be applied to the chest wall: twice-daily 1.5 Gy (2 fractions per day, at least 6 h between the fractions) with a total dose of up to 60 Gy (recommendation category: 3) (119, 120).

Breast Fibromatosis

The treatment is primarily surgical. If radical excision of the lesion is not possible (R1 or R2 resection), postoperative or definitive RT with 50–60 Gy dose can be administered (recommendation category: 2b) (121).

Male Breast Cancer

This is an uncommon condition (ratio in men:women is 1: 100–200). Evidences for female breast cancer is to be followed during treatment. For patients with operable breast cancer the primary treatment consists of radical mastectomy and removal of axillary lymph nodes (axillary block dissection/sentinel lymph node biopsy). The RT of the chest wall surgical area and the regional lymph nodes is identical to that recommended for female breast cancer cases. Breast-conserving surgery is rarely performed in men. The residual breast is irradiated after breast-conserving surgery (15).

Radiation Therapy for Locoregional Recurrences

Recurrence in the Ipsilateral Breast

- In the absence of prior RT, "salvage" mastectomy (standard treatment) is followed by postoperative RT according to the recommendations for primary treatment ("Chest wall irradiation after mastectomy") (recommendation category: 2a) (122). After administration of the full dose of RT, repeat irradiation with 40 Gy dose can be carried out (recommendation category: 2b).
- In the absence of prior RT, a second breast-conserving surgery is followed by postoperative RT according to the recommendations for primary treatment (see the first two paragraphs under "Chest wall irradiation after mastectomy") (recommendation category: 2a). After a prior full dose RT, repeated RT with perioperative interstitial brachytherapy or 3D conformal external RT can decrease the risk of a second local recurrence (recommendation category: 2b) (123–128). Doses: with HDR brachytherapy 22–36 Gy (in 5–10 fractions) (124, 126, 128), with PDR brachytherapy 45–50 Gy (124), or with teletherapy 45 Gy over 15 days (with a 2 × 1.5 Gy/day fractionation schedule) (123).

Chest Wall Recurrence

- If no adjuvant irradiation was administered after the first surgery, the entire ipsilateral chest wall must be irradiated (recommendation category: 2b) (122). Use of small fields is not recommended, since in the case of additional recurrences this leads to field adjustment issues and overdosing is unavoidable. The total dose is 50–54 Gy and the usual fractionation (2 Gy/day) is applied. After excision, the scar can be treated with an additional "boost" of 5 × 2 Gy. Extensive, contiguous recurrences are treated with palliative irradiation.
- If adjuvant irradiation was administered after the first surgery, the possibility of repeat irradiation is limited, since overdosing could lead to tissue necrosis or radiation ulcer. Palliative repeat irradiation is performed with individual dosing (usually 30–40 Gy) dependent on the dose of prior RT, using small fields without close fitting (recommendation category: 3) (122). Repeat irradiation using the CORT (Combined Operative and Radiotherapeutic Treatment) technique or HDR brachytherapy can be carried out to a maximal dose of 30 Gy (recommendation category: 3) (127).

Axillary Nodal Recurrence

- If no prior irradiation was used, a dose of 50–60 Gy with conventional fractionation (2 Gy/day) is recommended (recommendation category: 2b).
- In the event of prior irradiation, small-volume palliative irradiation is performed and individual dosing dependent on the dose of prior RT (usually 20–30 Gy) (recommendation category: 3).

Supraclavicular Metastasis (Recurrence)

- In the absence of prior RT, the entire region is irradiated with up to 50 Gy with conventional fractionation (2 Gy/day). The residual tumour can be treated with an additional "boost" of 5 × 2 Gy (recommendation category: 2B).
- Following a prior RT, a reirradiation dose of up to 30 Gy may be administered for palliative purposes (recommendation category: 3).

Radiation Therapy of Distant Metastases (Stage IV)

When administering palliative RT, the irradiated target volume, applied total dose and fractionation are less amenable to standardization than the same parameters in curative treatments. Individually tailored treatment is carried out, taking into consideration the extent of the disease, the life expectancy and general condition of the patient, and the dominant symptoms. In general, smaller total dose, single larger fractions (hypofractionation) and simpler irradiation methods are used, but when administering larger doses for palliative purposes, CT-based (if possible, 3D conformal) RT planning is recommended for the sake of healthy tissue protection.

For extracranial solitary metastases or low-volume oligometastatic disease with more favourable expected disease course (e.g., adrenal gland, bone or liver metastases) extracranial stereotactic RT may be an alternative to surgical treatment (metastasectomy).

Bone Metastases

- Solitary metastasis: usually 10 × 3 Gy or 5 × 4 Gy, over 1–2 weeks, possibly 1 × 8 Gy (recommendation category: 2a) (121).
- Multiple metastases: the purpose of irradiation is pain reduction and improvement of mobility; in such cases short treatment times are recommended (1×6–8 Gy, 2×4–5 Gy, 5×3–4 Gy, etc., open-field irradiation depending on the extent of the process and the size of the field) (recommendation category: 2a) (129).

Another alternative for the palliative treatment of multiple bone metastases is the use of open radioactive isotopes (strontium-89 chloride, yttrium-90 EDTMP, etc.) (recommendation category: 2a).

Brain Metastases

In cases with solitary brain metastasis or oligometastatic disease (2–4 foci) the recommended treatment is stereotactic radiosurgery (SRS) using a single fraction of 15–20 Gy dose or fractionated stereotactic RT (FSRT) in 3 to 5 fractions of 5–9 Gy without irradiation of the entire cranium (recommendation category: 2a), since irradiation of the entire cranium does not improve survival but decreases cognitive function and quality of life (130). Later on, eventual new solitary brain recurrences can be treated with stereotactic RT again by taking into consideration the previously treated target volumes and doses. For multiple brain metastases (>4) or brain metastases unsuitable for stereotactic treatment, whole brain irradiation is recommended. 10 × 3 Gy is sufficient to alleviate symptoms (recommendation category: 2a). For cases with a more favourable prognosis and patients in better general condition, 20 × 2 Gy can be administered to the whole brain, followed by a 5 × 2 Gy "boost" to the affected area using CT-based 3D conformal treatment planning (recommendation category: 2a) (129).

Mediastinal Metastasis

Palliative RT can eliminate the signs of the compression of the oesophagus or superior caval vein; the usual dose is 10 × 3 Gy, using two opposed fields (recommendation category: 2b) (129).

Skin Metastases

Irradiation should be planned in line with the extent of the disease and the number and size of the foci (recommendation category: 2b) (129).

Intraocular and Orbital Metastasis

CT-based (if possible, 3D conformal) RT planning is applied and the dose is usually 10 × 3 Gy (recommendation category: 2b) (129).

This is part 2 of a series of 6 publications on the 1st Central-Eastern European Professional Consensus Statements on Breast Cancer covering imaging diagnosis and screening (131), pathological diagnosis (132), surgical treatment (133), systemic treatment (134), radiotherapy (present paper) of the disease and related follow-up, rehabilitation and psycho-oncological issues (135).

AUTHOR'S NOTE

The consensus document contains product placement without the intention of advertising. Each complex molecular test is unique, and although these can be described without indicating their name (for example with the number of genes tested), not everyone will necessarily understand what this refers to. For this reason, and adopting the practice used in some of the source works, the tests are listed under their trade name.

AUTHOR CONTRIBUTIONS

CP, JF, and ZK have provided the concept of the manuscript and written the manuscript. All authors have searched and collected clinical evidences and references for the consensus statement. All authors have revised the manuscript.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Systemic Treatment of Breast Cancer. 1st Central-Eastern European Professional Consensus Statement on Breast Cancer

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This text is based on the recommendations accepted by the 4th Hungarian Consensus Conference on Breast Cancer, modified based on the international consultation and conference within the frames of the Central-Eastern European Academy of Oncology. The professional guideline primarily reflects the resolutions and recommendations of the current ESMO, NCCN and ABC5, as well as that of the St. Gallen Consensus Conference statements. The recommendations cover classical prognostic factors and certain multigene tests, which play an important role in therapeutic decision-making. From a didactic point of view, the text first addresses early and then locally advanced breast cancer, followed by locoregionally recurrent and metastatic breast cancer. Within these, we discuss each group according to the available therapeutic options. At the end of the recommendations, we summarize the criteria for treatment in certain rare clinical situations.

Keywords: early breast cancer, locally advanced breast cancer, adjuvant treatment, neoadjuvant treatment, metastatic breast cancer, inflammatory breast cancer, guideline

INTRODUCTION

Since the 3rd Hungarian Breast Cancer Consensus Conference (1), new evidence based on clinical trial results has been published, which has justified updating the 2016 recommendation. In addition to classical prognostic factors, certain multigene tests, which should be incorporated into the recommendations, will play an important role in therapeutic decision-making.

This professional guideline primarily reflects the positions and recommendations of ESMO (2), NCCN (3), ABC5 (4), and the St. Gallen Consensus Conference (5) (other sources are indicated in the appropriate section). From a didactic point of view, the text first addresses early and then locally

TABLE 1 | Hormone sensitivity categories of early breast cancer (Ref to pathology chapter).

Hormone sensitivity	Allred score	Recommended treatment
Highly hormone-sensitive	Allred 6[a]-7-8	Endocrine therapy is recommended [alone or after chemotherapy in combination (±anti-HER2)]
Hormone resistant	ER- and PR-negative (Allred 0 and 2)	Endocrine therapy is ineffective, chemotherapy (±anti-HER2) is required
Uncertain hormone sensitivity	Allred 3-5	Primarily chemotherapy ± anti-HER2, followed by endocrine therapy

[a]*Allred score of 6 may be due to: 1) 10% to 1/3 of cells shows strong staining; 2) between 1/2 to 2/3 of cells shows moderate staining; 3) >2/3 of cells shows weak staining. See: Pathological diagnosis, work-up and reporting of breast cancer. Pathology recommendations from the 4th Consensus Conference on Breast Cancer.*

advanced breast cancer, followed by locoregionally recurrent and metastatic breast cancer. Within this structure, we discuss each group according to the available therapeutic options. At the end of the recommendations, we summarize the criteria for treatment in certain rare clinical situations and propose the use of new protocols. Our recommendations basicly use the ESMO evidence and recommendation categories (and other, e.g., NCCN categories are indicated separately).

To achieve acceptable therapeutic results, it is important to treat patients with breast cancer in specialized institutions or departments where enough early-stage breast cancer patients are encountered each year (6). The European recommendation sets this number at 150 new cases per year (III.A).

Application of multidisciplinary principles is essential (7). Therapeutic decisions should be based on tumour board decision, involving representatives of the relevant specialties such as surgeons, pathologists, radiotherapists, radiologists, medical oncologists (and in certain cases psychologists) as well as the patient, or her legal representative/guardian as substitute decision-maker, and the patient's decision-making support system. It is advised to involve clinical geneticist and fertility preservation specialist, too (in certain countries it is mandatory). The patient must be provided with the appropriate information on which to base her/his decisions. Due to their predicament, patients only retain a fraction of the information provided to them, therefore it is important to communicate in an easy-to-understand format with repetitions, to answer any of the patient's questions, and in addition to passing verbal information to provide the patient with supplementary information in written format and patient-centred websites (V.A).

Some recommendations in the professional guidelines are considered off-label treatments at the time of the completion of this text; these are indicated with a "§" symbol.

EARLY BREAST CANCER

The primary decision point of early breast cancers is whether the tumour contains an invasive component.

Adjuvant systemic therapy decision in early breast cancer is based on known prognostic and predictive factors and patient preferences. Within this framework, the most important clinical task, beyond the assessment of the extent of the disease or identification of certain molecular subgroups, is to include a weighing of the expected risks and benefits of a given therapy. From this standpoint it is essential to pinpoint the therapies to which the tumour is expected to react or resist. Therefore, one of the most important factors is to determine the hormone sensitivity of the tumour (see **Table 1**). A tumour is considered hormone-sensitive if the oestrogen and/or progesterone receptor (ER/PR)—hereinafter hormone receptor (HR)—content is at least 1% positive cells (8, 9), even though the success of endocrine treatment is questionable in the presence of values less than 10%. It is important to note that the ER-negative/PR positive phenotype is exceedingly rare; in most cases, it is caused by a laboratory error or a false negative ER reading or a false positive PR reading. Therefore, a repeat of the tests should be requested (10).

Additional factors influencing the treatment:

- Tumour staging according to the TNM classification system,
- Pathological features beyond hormone-receptor status HER2 status, histological type, proliferation characteristics as grade, mitotic activity index (MAI), and Ki67,[1]
- Patient characteristics: biological age, general condition (performance status), comorbidities, organ reserves, previous treatment and preferences of the patient, availability of the medication, and results of genetic tests (gene expression profiles scoring and germ line mutation such as BRCA 1/2 among others, as indicated) (V.A).

In the next section we describe the treatment of breast cancer based on staging derived from the TNM classification system. A more accurate prognostic classification of TNM is represented by the AJCC prognostic staging that also takes differentiation into account (eighth edition) (11), and this is the same staging that is referenced in the Pathology chapter of the Consensus document. In the following section, tumours are classified according to anatomical stages. Classification systems such as NPI (Nottingham Prognostic Index) or the PREDICT tool (https://breast.predict.nhs.uk/) provide important additional prognostic information to assist therapeutic decision-making.

Non-Invasive Breast Cancer (Stage 0, Tis, N0 M0)

- According to the combined assessment of two randomized studies, after breast-conserving surgery and radiation

[1]Urokinase plasminogen activator/plasminogen activator-inhibitor-1 (uPA/PAI-1) is also an option, used in some countries).

TABLE 2 | Surrogate definitions of the intrinsic subtypes of breast cancer (2).

Intrinsic subtype	Clinicopathological surrogate definitions
Luminal A "luminal A-like"	- ER-positive - HER2-negative - Ki67 low - PR elevated - Low-risk molecular signature (if available)
Luminal B "luminal B-like (HER2-negative)"	- ER-positive - HER2-negative - and - Ki67 high[a] and/or - PR low and/or - High-risk molecular signature (if available)
"Luminal B-like (HER2-positive)"	- ER-positive - HER2-positive - Any Ki67[b] - Any PR
HER2 "HER2-positive (non-luminal)"	- HER2-positive - ER and PR missing
"Triple-negative"[c]	- ER and PR missing - HER2-negative[c]

Based on the recommendations of the 2013 St. Gallen Consensus Conference (162).
[a]Ki67 values should be evaluated based on local laboratory values: for example, if the median Ki67 value in the laboratory is 20% in HR-positive disease, then values of 30% or above are to be read as high, and values equal to or less than 10% should be read as unequivocally low. (However, since the median Ki67 values of each group determined by the laboratory are usually not known, the recommendation is not entirely reliable, and the values should be taken as general guidelines.)
[b]The recommended cut-off value is 20%; quality control programs are essential tools for laboratories for the evaluation of reports.
[c]There is an 80% overlap between the "triple-negative" and intrinsic "basal" subtype.

therapy (if any), 5 years of adjuvant tamoxifen therapy (20 mg/day) administered for hormone-sensitive tumours—independently from menopausal status - can decrease the incidence of invasive and non-invasive local recurrences as well as the incidence of secondary (contralateral) breast tumours (I.A).

- Compared to tamoxifen, anastrozole further decreased the incidence of breast cancer events, but no benefit was shown in terms of disease-free or overall survival (NRG Oncology/NSABP B-35 study) (12). With emphasis that AI are exclusively for postmenopausal patients, indication for aromatase inhibitor (AI) is like that of tamoxifen (I.B). Beyond menopausal status a different safety profile should be considered when choosing this medicinal product.
- If mastectomy is performed, the aim of postoperative treatment is to decrease the risk of a contralateral breast cancer, and therefore no additional systemic treatment is indicated following double mastectomy. When recommending adjuvant endocrine therapy (ET) it should be considered that—although the likelihood is small—clinically significant complications (such as endometrial cancer, thromboembolism, osteoporosis, and cardiovascular complications) may develop, and this treatment has no confirmed effect on survival.
- The prognosis of the disease is particularly good. At the 20 years mark the likelihood of an invasive cancer is 6% in the affected breast (breast-conserving surgery) and the contralateral breast alike, and tumour-specific mortality is 3%. The risk is higher for young (under 35 years old) patients if their tumour is poorly differentiated (grade 3, "high grade") or oestrogen receptor negative (13).

Recommendation

- Chemotherapy and anti-HER2 therapy are not indicated.
- Aromatase inhibitor (anastrozole) and tamoxifen are both suitable as endocrine therapy (tamoxifen is preferable, AIs are not available in all countries.) Menopausal status should be considered.
- For radiotherapy, please see radiotherapy guideline.

Early-Stage Invasive Breast Cancer (Stage I–II-IIIA [<N2]), or Potentially Resectable Stage IIIB

Criteria for Choosing Neoadjuvant and Adjuvant Systemic Treatments

- Decision-making on the use of perioperative (neoadjuvant or adjuvant) treatments has three steps.
  - The first step is the assessment of prognosis (See **Supplementary Appendix S1**).
  - The second step is assessment of predictive factors which will guide treatment choice. These two important factors will define the expected relative and absolute benefits of the treatment.
  - The third step is to consider potential short- and long-term adverse events as well as the patient's characteristics and preferences into account (V.A).

- The prognosis of the tumour is defined mainly by its extent and biological characteristics. The prognostic factors of early invasive breast cancer include primary tumour size (T), nodal status (N), histological grade (G), proliferation rate (e.g. Ki67/MAI), HR and HER2 status, peritumoral vascular invasion, and recently, specific gene expression profile tests (genomic profiles). The assessment of prognosis is helped by the Nottingham Prognostic Index (14-17), tools analysing certain databases (PREDICT tool) (14, 18-21), and tumour genetic tests (see below).
- The expected efficacy of systemic treatment is indicated by the biological characteristics of the tumour (predictive factors). Recommendation of certain treatments should be based on treatment-oriented classification (**Table 2**) defined by the endocrine sensitivity (**Table 1**), HER2 status and proliferation characteristics of the tumour. Prognostic and predictive factors serve as a basis for deciding whether the therapeutic benefit of a given systemic treatment modality outweighs the risks due to its potential side-effects. As an example, for a patient with a good prognosis, clinically insignificant therapeutic gains can be expected from systemic treatment (primarily chemotherapy).
- Endocrine therapy is justified for all HR-positive conditions (ER and/or PR expression ≥1%) (I.A). In some countries adjuvant hormone treatment is recommended for all patients with HR-positive tumours without exceptions. Omission of endocrine therapy may be considered in other countries when the prognosis is remarkably good (the rate of long-term relapse is below 5%) (V.E).
- Chemotherapy may be omitted for a large proportion of HR-positive tumours, and its application is indicated primarily in more extensive and poorly differentiated tumours. Its use is usually justified in HR-negative cancers.
- Chemotherapy and anti-HER2 therapy are recommended for most HER2-positive cancers.
- Concomitant treatments:
  - Concomitant administration of chemotherapy and endocrine therapy is not recommended. The only exception is the administration of GnRH analogues to preserve fertility.[§]
  - Anti-HER2 therapy can be given concomitantly with taxane chemotherapy but not with anthracyclines (I.a) due to increased risk of cardiotoxicity. Also, it can be combined with radiation therapy[§] and endocrine therapy; radiation therapy and endocrine therapy can also be administered concomitantly. Tamoxifen may exacerbate irradiation-induced pulmonary fibrosis, it could be considered for parallel application.
  - When adjuvant chemotherapy is indicated, it precedes radiation therapy.
- In recent years the classification of luminal A-like, luminal B-like, HER2-positive, and triple-negative has become the preferred method of decision-making in determining therapy. This classification derives from gene-expression profile results, where the tumours were grouped as luminal A, luminal B, HER2-enriched (HER2-E), basal-like and normal-like (normal-like is not considered a true, intrinsic subtype, as it originates from a tumour sample that includes a significant amount of normal breast tissue, thus representing a mix of normal tissue and tumour cells) (**Table 2**). Although multi-parametric genomic tests that serve as a basis for the classification are not widely available, immunohistochemical (IHC) tests can provide an approximation of the genome-based classes.[2]

Additional factors that must be taken into account during the therapeutic decision include potential short-term and long-term side-effects (e.g., chronic alopecia, neuropathy, cardiac and vascular toxicity, second malignancy, infertility, and classical endocrine side-effects) as well as the biological age, general condition, comorbidities, and preferences of the patient.

- Adjuvant treatment should be started between 3–6 weeks after surgery but no later than the 12th week, because its efficacy declines significantly after this time point (I.A). Neoadjuvant therapy should be started after determining the diagnosis (based on the result of the core biopsy) and preferably within 4 weeks after mammography. It is preferable to have the staging results in hand before starting treatment, but a delay in obtaining these results should not delay the start of the treatment (V.A).

The treatment-oriented grouping recommended by current treatment guidelines differentiates four groups based on HR status, HER2 status and proliferation. The efficacy of the various treatment modalities is different in each subgroup (**Table 2**).

The Role of Gene Expression Assays and Other Molecular Diagnostic Tests in Determining the Choice of Adjuvant Chemotherapy and Endocrine Therapy

In addition to prognostic factors used to estimate risk of relapse and survival, molecular genetic tests (Oncotype DX®, MammaPrint®, PAM50 ROR®, Breast Cancer Index®, and EndoPredict®) add additional prognostic and possibly predictive information.

The available tests provide a variety of results. In general, clinical studies have been carried out in patients with stage pT1-2 and pN0 as well pN1 disease.

- The independent prognostic value of these tests is accepted and in the case of two tests (OncotypeDX® and Mammaprint®) it is also supported by robust evidence (I.A).
- Regarding chemotherapy sensitivity (predictive value) OncotypeDX® is the only test supported by evidence at present (I.A).

Recommendation (On the Application of Chemotherapy)

- Theoretically, if we want to make the best decision on the application of CT, all patients should be tested with Oncotype DX®.

[2]When IHC is used for classification, it is recommended to apply the "-like" suffix in order to differentiate genome- and IHC-based definitions (e.g., luminal A-like).

- The OncotypeDX® test is recommended in the case of ER-positive, HER2-negative, primarily stage pT1c-pT2 N0-N1mi M0 patients with "moderate risk" (3.4–5.4 based on NPI) early breast cancer patients, if the available tests results and other criteria do not allow the oncology team to define a clear therapeutic plan and the patient accepts chemotherapy as long as that is supported by the results of this test.
  - Stage pT1bc-T2pN0 (HR-positive/HER2-negative) patients (22) were included in the TAILORx study.
    - In general, an RS (recurrence score) below 26 indicated that the chemotherapy had no added value.
      - however, reduction in the number of distant metastases in response to chemotherapy was detected in the under 50 age group with RS 16–25, therefore chemotherapy should be considered for these patients (it provides 1.6% benefit in the RS 15–20 range and 6.5% benefit in the RS 21–25 range).
    - In the range of RS 26–30 chemotherapy should be considered and rather recommended. For values above RS 30 the benefits of chemotherapy were clear (27% benefit) (23).
  - Based on the above data the simplified recommendation is as follows:
    - RS 0–25: endocrine therapy (with additional ovarian suppression for patients younger than 50), but chemotherapy can be considered in individual cases.
    - RS 26 and above: chemotherapy—the chemotherapy regimen is based on the patient's general condition and preferences.
  - Lymph node micrometastasis is classified as N1 by OncotypeDX®. Accordingly, in stage N1 (mic and 1–3) the following are recommended based on RS score.
    - 0–25: in postmenopausal patients chemotherapy is not recommended.
    - 0–25: in premenopausal patients chemotherapy should be considered, however, the therapeutic gain can be derived from ovarian suppression effect of chemotherapy. The absolute gain was more pronounced with RS 14–25.
    - Above 25: chemotherapy is recommended.
- In cases of favourable histology (tubular, mucinous, papillary), the markedly favourable survival outlook means that chemotherapy is generally not required, and a multigene test is unlikely to be required.
- Limited data available from male patients (24) and in neoadjuvant situation, however the prognostic value of OncotypeDX is likely.

The availability of hormonal resistance biomarkers that can be confirmed by other molecular genetic methods has been steadily increasing (e.g., PIK3CA mutation, ESR1 and AKT mutations, HER2 and FGFR alterations, etc.). Currently their practical significance is mainly limited to advanced/metastatic disease, but thanks to the increasing availability of the promising liquid biopsy method all indicators point to their future use in the adjuvant and follow-up periods (25).

Criteria for Choosing Adjuvant Endocrine Therapy and Therapeutic Options

ET has an essential role in HR-positive and HER2-negative tumours. When choosing ET, menopausal status and risk should be considered (for relevant definitions see **Supplementary Appendix S2**). Since a variety of endocrine therapies with nearly identical effectiveness but partially different side-effect profiles are currently available, optimal strategies can be devised for each patient. The therapeutic plan should depend on the risk of relapse, molecular characteristics and histological subtypes of the tumour, the risk of contralateral breast cancer, age, especially menopausal status and patient's preferences.

- In premenopausal women, ovarian ablation–if necessary—should be carried out using a reversible method (LHRH/GnRH analogue) due to the risks of prolonged oestrogen depletion [e.g., osteoporosis, (26)] and to preserve fertility for potential future childbearing (27) (II.B). Laparoscopic adnexectomy should be offered as an alternative, after properly informing the patient.
- Aromatase inhibitor (with LHRH/GnRH analogue if premenopausal) or tamoxifen (with or without LHRH/GnRH analogue if premenopausal) can be used as adjuvant endocrine therapy in both premenopausal and postmenopausal women, and their use should be adjusted according to the characteristics of the tumour and the side-effect profile of the administered medication (28, 29) (I.A). The menopausal level of oestrogen should be checked regularly during LHRH-analogue therapy.
- In HR-positive and HER2-positive cases, ET should be added to HER2 inhibitor therapy following chemotherapy (I.A).
- In HER2-positive and luminal B-like cases use of an aromatase inhibitor is preferable (with LHRH/GnRH analogue if premenopausal) (28, 29).
- Tamoxifen can be recommended as sole therapy for 5 years for low-risk, stage I hormone-sensitive breast cancer in both premenopausal and menopausal women (5).
- According to the SOFT study, ovarian ablation potentiates the effects of both tamoxifen and aromatase inhibitor in terms of distant metastasis-free survival (30, 31) (II.B).
- According to the SOFT and TEXT (27,29–34) studies, exemestan + LHRH/GnRH analogue (triptorelin)—compared to tamoxifen + LHRH/GnRH analogue (triptorelin)—improves disease-free survival and metastasis-free survival during premenopause, especially in high-risk patients. The greatest benefit can be expected in the high-risk patient group (<35 years of age, high grade/high Ki67 value, or positive lymph node status); this therapeutic benefit was especially compelling in patients who had already received chemotherapy (31) (I. A).
- Tamoxifen administered for 10 years to high-risk (primarily lymph node positive) premenopausal women provided a survival benefit compared to 5-year treatment (32, 33) (I.A).

5 years of AI therapy following 5 years of tamoxifen therapy also decreases disease-free and overall survival in lymph node-positive disease. The currently recommended period of aromatase inhibitor administration during extended endocrine therapy is 5 years, but studies in progress are evaluating this therapy beyond the 5 year period (32, 34, 35). According to a recent meta-analysis (36), compared to tamoxifen therapy or tamoxifen-aromatase inhibitor switch treatment strategies, extended aromatase inhibitor therapy provided significant advantage in terms of relapse-free survival (RFS) however did not reach a significant level in patients who were previously treated with AI monotherapy. The benefit increased with lymph node positivity, but there was also a significant increase in the number of events affecting the bones. Required check-ups before and during aromatase inhibitor therapy include routine bone density measurements every 2 years, or more frequently if the patient has osteoporosis.

Adjuvant ET Recommendations—Premenopause

- Tamoxifen for 5 years.
- Tamoxifen for 10 years.
- Aromatase inhibitor + LHRH analogue for 5 years ± ([extended] tamoxifen 5 years).
- Tamoxifen for 5 years + LHRH analogue (for 2–5 years) (± [extended] tamoxifen for 5 years).
- Tamoxifen (±LHRH analogue) for 5 years, and once patient is in stable menopause 5 years of aromatase inhibitor (however, menopause status must be confirmed).

Adjuvant ET Recommendations—Postmenopause

- Tamoxifen for 5 years if patient is low risk (stage I).
- Aromatase inhibitor for 5 years.
- Aromatase inhibitor and tamoxifen in any order (switch regimen)—2–3 years/3–2 years.
- The extended ET should be followed by tamoxifen or aromatase inhibitor according to prior adjuvant ET and side-effect profile.

During perimenopause, aromatase inhibitor therapy can induce stimulation of the ovaries, therefore hormone tests (repeated FSH and oestradiol tests are recommended) [I.a]) to increase the safety of the chosen therapy for women aged <60 years in menopause (see also the criteria for menopause, **Supplementary Appendix S2**). When endocrine therapy is started close to the anticipated time of menopause but still in premenopause—and the patient's hormone tests later confirm postmenopause—the patient could be switched from tamoxifen to aromatase inhibitor therapy without the addition of LHRH analogue.

For HR-positive and HER2-positive cancers the standard therapy is chemotherapy followed by endocrine therapy plus a total of 1 year of trastuzumab treatment (I.A). If the patient is high-risk, taxane based chemotherapy is combined with dual anti-HER2 blockade (trastuzumab + pertuzumab if available), followed by endocrine therapy along with dual anti-HER2 blockade up to 1 year (see below). Consider extended neratinib therapy for one additional year in high-risk tumors, if available (also see later).

Criteria for Choosing Adjuvant Chemotherapy

The requirement for adjuvant treatment is based on the risk of relapse. Clear indications for cytotoxic chemotherapy include the following parameters that indicate high risk:

- Basal type/triple-negative or HER2-positive breast cancer (larger than 10 mm, at least pT1c) and/or pN1 (1–3 metastatic lymph nodes). Rare exceptions include such histological subtypes as secretory or adenoid cystic carcinoma (few available data, chemotherapy only in case of N+).
- High-risk luminal HER2-negative tumours (e.g., result of multigene test) (I.A).
- N2-N3 lymph node status (4 or more metastatic lymph nodes).

In HR-positive and HER2-negative disease other indications:

- G3; intermediate/high proliferation, high Ki67.
- Low HR content (less than 10% of tumour cells show positivity).
- pN1 status.
- Lymphovascular invasion.
- Large tumour mass (pT3-4) (based on the assumption that chemosensitive or endocrine resistant clones are present due to intratumoural heterogeneity).
- Age less than 35 years should not be the exclusive reason to give chemotherapy if other intermediate or high-risk factors are not present. In grey zone, multigene tests (if available) can be used to assist in determining the proper adjuvant therapy.
- Chemotherapy is primarily recommended for triple-negative (TN), HER2-positive and luminal B-like HER2-negative type tumours (I.A). The absolute benefit of chemotherapy is more pronounced in case of ER-negative tumours.
- The choice of chemotherapy depends on the expected efficacy but also depends on long-term toxicity of the chosen treatment, the biological age, general condition, comorbidities, and preferences of the patient (2).
- Most luminal A-like tumours do not require chemotherapy; the exception are cases with large tumour mass or extensive lymph node involvement (pT3-4 or pN2-3). According RxPONDER trial results in selected cases with pT3pN0-1 tumor chemotherapy may be avoided with RS (OncotypeDX®) (37, 38).
- Chemotherapy can be administered when the indication is uncertain (with all clinical and pathological factors known), and the result of the gene expression test, for example OncotypeDX® are indicating intermediate or high risk for relapse. This was discussed above in detail.

Recommendation

- The standard chemotherapy treatments include anthracycline and/or taxane preferably as sequential therapy.
  - The most commonly used anthracycline-containing treatments are doxorubicin/adriamycin-cyclophosphamide

(AC) and epirubicin-cyclophosphamide (EC) for four cycles (I.A) (3).
  - The most used taxane based chemotherapy in sequence with anthracyclines are mono-docetaxel for four cycles or mono-paclitaxel given once weekly for 12 weeks (3).
  - 5FU-containing triple drug combinations (FAC/FEC) should no longer be used routinely.
  - Taxane-based treatments (without anthracycline), such as docetaxel/cyclophosphamide (TC) (39), can be alternatives to anthracycline based-therapies. According to the US Oncology Trial 9735, in non-selected stage I-IIIB patients the docetaxel-cyclophosphamide combination is significantly more effective in terms of both DFS and OS than the doxorubicin-cyclophosphamide combination.
  - Treatments without anthracycline can be used in the presence of significant risk of cardiac complications (I.A).
  - The efficacy of the 6×CMF protocol is identical to that of 4×AC/EC, but its toxicity is greater (II.B)(40). The use of anthracyclines is preferred to treatment with the CMF regimen, because they are significantly more effective both in terms of relapse and survival given in the same number of cycles (41) (I.A).
- The inclusion of taxanes resulted in a moderate increase in therapeutic efficacy independently of age, lymph node status, grade, and receptor status (I.A). Overall, anthracycline- and taxane-based chemotherapy protocols decrease breast cancer mortality by a third.
- The sequential administration of taxanes and anthracycline is more beneficial and less toxic (due to reduced cardiotoxicity) than concomitant administration (I.A).
  - The recommended dosing frequency is once a week for paclitaxel and once every 3 weeks for docetaxel.
  - According to a randomized trial, the taxane/anthracycline order may be more effective than the usual anthracycline/taxane order, although both are acceptable (42) (I.A).
- In the absence of significant prospective data, the routine treatment of TN and/or BRCA1/2 positive tumours with platinum-containing therapies—even though they seem highly effective—is not recommended.
- Dose-dense (dose-intensified) treatments (supported by the administration of G-CSF) are primarily recommended for tumours with high proliferation rates (I.A). Based on long-term analyses, dose-intensified treatments are more effective than treatments with conventional schedules.
  - One such therapy is the AC—P protocol applied every 2 weeks with filgrastim support (CALGB 9741 trial) (43).
- If there is a high risk of recurrence and/or axillary lymph node positivity is confirmed, then sequentially.
  - 4×AC—12× (weekly) paclitaxel (E1199 trial) (44).
  - Or concurrently (6×docetaxel + AC, "TAC"/TEC) dosage is also possible (BCIRG001 trial) (45); in the latter case filgrastim prevention is used due to rates of febrile neutropenia in excess of 20% (not recommended in all countries).
  - According to the NSABP B-38 trial (46) (TAC vs. AT vs. AC—T)—which only included N0-1 patients—the sequential AC—T arm produced significantly better results in terms of both DFS and OS than the other two arms; the efficacies of the other two arms were identical. This trial also confirmed that survival parameters were much better when chemotherapy-induced amenorrhoea developed than in the absence of this side-effect.
- Triple-negative disease also warrants the use of anthracycline and taxane.
- The indication of chemotherapy for patients above 70 years is determined on an individual basis, and the biological age, comorbidities, and preferences of the patient should be included in the decision-making process. Only limited data are available from clinical trials. Medications should be used at full dose if possible. A geriatric status assessment is recommended before the planned treatment is initiated.
- Concomitant administration of chemotherapy and endocrine therapy is not recommended, with the exception of GnRH analogues used to preserve ovarian function (47) (I.A).
- Anti-HER2 treatment can be routinely combined with non-anthracycline-containing chemotherapy, endocrine therapy, and radiation therapy.
- If both chemotherapy and radiation therapy are required, chemotherapy must precede radiation therapy (48, 49). The exception to this rule is:
  - Capecitabine treatment following adjuvant radiation therapy of patients with residual tumour after neoadjuvant chemotherapy (50) (II.A).
- The use of equipment for administering venous systemic treatment—e.g., port catheter, indwelling peripheral cannula—should be considered, and decided on an individual basis for each patient, taking into consideration both their benefits and potential complications.
- On the postoperative side, all interventions that increase lymph circulation are associated with an increased risk of lymphoedema. Therefore, necessary interventions (such as blood pressure measurements, blood draw, and infusions) should be primarily performed on the contralateral extremity (III.B).
- High-dose chemotherapy with stem cell transplantation is not recommended.

The Treatment of Early HER2-Positive Tumours

For early-stage (stage II-III) HER2-positive breast cancers the preferred treatment is neoadjuvant therapy containing HER2 targeted therapy, and the postoperative adjuvant treatment is determined by the degree of pathological response. However, for small and lymph node-negative tumours (stage I) primary surgery is also acceptable, and it is followed by adjuvant treatment containing anti-HER2 treatment (**Figure 1**).

Recommendations for neoadjuvant/primary systemic treatment of HER2-positive breast cancers:

For HER2-positive tumours the anti-HER2 therapy must be started as part of the primary systemic treatment.

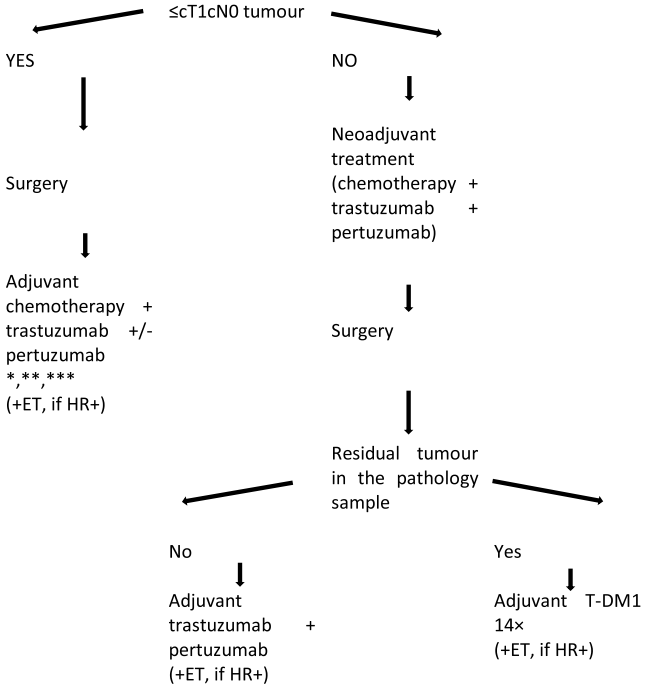

FIGURE 1 | Treatment algorithm of HER2-positive early breast cancers. *Adjuvant administration of trastuzumab and pertuzumab for a total period of 1 year is recommended; this also includes the neoadjuvant cycles. **Adjuvant pertuzumab is recommended for high-risk patients (lymph node positivity). *** In pT1a cases neither chemotherapy nor anti-HER2 therapy is required, except for ET in the event of HR-positivity.

- The standard base therapy is perioperative trastuzumab therapy for 1 year.
- Dual HER2 inhibition is recommended from stage II, using trastuzumab and pertuzumab (primarily for HR-negative cases) (51-54).
- HER2 inhibitor therapy should be started together/concurrently with taxane-containing neoadjuvant chemotherapy.
  - This means four cycles of (epi-) adriamycin-cyclophosphamide (AC/EC) treatment followed by weekly paclitaxel (12 cycles) OR docetaxel (4 cycles, every 3 weeks) AND trastuzumab ± pertuzumab treatment.
- Trastuzumab can be administered intravenously or subcutaneously.
- Concomitant administration of anti-HER2 therapy and anthracycline is not recommended due to increased cardiac risk.
- A non-anthracycline-containing protocol can be used in the presence of increased cardiac risk or in very young patients—e.g., Six cycles of TCH (docetaxel, cyclophosphamide, trastuzumab) or in the neoadjuvant setting PHTC (pertuzumab + trastuzumab + docetaxel + carboplatin) (TRYPHAENA and KRISTINE trials) (51, 52). Optimal use of the de-escalation regimens is not yet defined based on limited available data e.g., ADAPT-HR-/HER2+ (55), results of more studies (CompassHER2 (56) and DeCrescendo (NCT04675827)) should be awaited.
- All planned neoadjuvant chemotherapy (+ the associated concomitant anti-HER2) treatment cycles should be scheduled before surgery to increase the chance of pCR. The rest of the anti-HER2 treatments are administered as adjuvant therapy.
- Achieving pCR predicts a good prognosis with improved disease-free and overall survival and therefore should be the objective of treatment.

Recommendations for choosing adjuvant therapy following primary systemic chemotherapy + anti-HER2 treatment.

- If the patient achieves pathological complete response (pCR) in response to neoadjuvant therapy, continuation of trastuzumab + pertuzumab or trastuzumab monotherapy is recommended as adjuvant treatment, for a total of 1 year (including the neoadjuvant cycles). Based on the results of the APHINITY trial (57) the benefit of dual inhibition was primarily detected in lymph node positive patients (II.B). If there is residual invasive disease in the breast and/or the axilla, then surgery should be followed by the administration of 14 cycles of ado-trastuzumab emtansine (T-DM1) if available, because—based on the data of the KATHERINE trial (58)—significant and clinically relevant increase in disease-free survival can be achieved compared to adjuvant trastuzumab (II.B). If the T-DM1 has to be interrupted, e.g. due to toxicity, then the adjuvant treatment should be completed with trastuzumab (±pertuzumab) until the 1 year time point (**Figure 1**). In this trial most patients were administered radiation therapy and endocrine therapy concomitantly with postoperative trastuzumab or T-DM1 treatments if the tumour was HR-positive. The investigators could not detect any increase in treatment-associated toxicity associated with these concomitant treatments.
- According to the results from several neoadjuvant trials, the combination of trastuzumab and lapatinib[$] (59) or trastuzumab and pertuzumab dual HER2 blockade[$] (53, 54) can induce significant pCR even without chemotherapy, but the magnitude of the response lags behind that induced by combinations with chemotherapy. Currently there is no known biomarker that would selectively indicate patients who are suitable for treatment with biologic therapy only (without chemotherapy) therefore it is not recommended.

Recommendations for adjuvant only anti-HER2 therapy:

- The combination of chemotherapy and anti-HER2 therapy is required starting at pT1c status and lymph node positive disease (trastuzumab ± pertuzumab). It can also be recommended for the treatment of pN0 tumours measuring less than 1 cm in size (primarily pT1b, ER-negative) (IV.B).
  - For very early, lymph node negative, low-risk disease with size below 5 mm (pT1a pN0) close observation can be considered, but administration of trastuzumab +

paclitaxel is also supported (not recommended in all countries).
- Addition of pertuzumab to trastuzumab is primarily recommended for high-risk disease (lymph node positivity) as shown by the results of the APHINITY trial (57).
- Concomitant administration of anti-HER2 treatments and anthracycline therapy is not recommended.
- According to the principles of sequential treatment, four cycles of AC/EC, followed by 12 weeks of paclitaxel or four cycles of docetaxel + trastuzumab ± pertuzumab (HER2 targeted therapy started with taxane) treatment should be preferred.
- Chemotherapy is followed by trastuzumab ± pertuzumab therapy for a total of 1 year (I.A).
- In Stage I, non-anthracycline-containing, low toxicity TH (paclitaxel + trastuzumab 12×) treatment is also a viable option (60), especially in the presence of comorbidities (II.B).
- If the administration of anthracycline is to be avoided due to increased cardiac risk, then six cycles TCH(P) treatment (docetaxel + carboplatin + trastuzumab ± pertuzumab) or docetaxel + cyclophosphamide + trastuzumab can be recommended as non-anthracycline-containing options (II.B).
- Regular (or in the absence of problems, quarterly) cardiac follow-up (typically echocardiography) is required at the beginning of and during adjuvant trastuzumab ± pertuzumab treatment.
- After the completion of chemotherapy, endocrine therapy should be started concurrently with adjuvant anti-HER2 treatment (I.A).
- Adjuvant trastuzumab can be administered intravenously or, alternatively, in the fixed dose subcutaneous formulation, which is of equivalent efficacy and similar side-effect profile, and which does not require a loading dose. The latter method is more beneficial for the patient and is easier to administer (61-63). Subcutaneous trastuzumab can be given as monotherapy or as a combination with fix-dose subcutaneous pertuzumab (64).
- For high-risk, HR-positive, HER2-positive, lymph node-positive breast cancer, if available an extended adjuvant HER2 inhibitor option is the administration of neratinib for 1 year following trastuzumab-containing treatment[$] (65). The benefits and toxicity profile of this treatment for patients receiving prior pertuzumab or adjuvant T-DM1 are not known, and therefore it is not recommended for this patient group.

PREOPERATIVE/NEOADJUVANT SYSTEMIC THERAPY (STAGES IIA-IIB-IIIA(N2)—UNRESECTABLE IIIB-IIIC)

When mastectomy is necessitated by large tumour size in cases of locally/regionally advanced (unresectable) and large resectable invasive tumours, primary (neoadjuvant) systemic treatment (PST) is recommended to reduce the extent of surgical intervention. The therapeutic response to PST has prognostic value and assists in choosing postoperative therapy.

All systemic therapeutic modalities (chemotherapy, endocrine and molecularly targeted therapy) used as adjuvant treatments can also be administered pre-operatively.

The advantage of PST is that systemic therapy can be started at the earliest time point and its efficacy can be measured based on tumour regression, and it can be used as an *in vivo* chemosensitivity test and thus serves as a starting point for treatment modification (if needed). Another advantage is that it decreases the risk of chemo resistance. By down staging the primary tumour or even axillary lymph node metastases, it can make originally unresectable tumours resectable, and can also moderate the extent of surgery and/or radiation therapy.

Pathological complete response (pCR) is a basic parameter indicating the efficacy of primary/neoadjuvant systemic therapy and predicting both the expected prognosis and survival. According to a widely used definition, pCR means that in response to neoadjuvant therapy an invasive tumour (or in some cases, *in situ* tumour) becomes undetectable in the surgically resected specimen at the site of the primary tumour and the lymph nodes (ypT0/ypTis ypN0). (For definitions, please see the chapter on pathology).

Neoadjuvant therapy is proven to be as effective as adjuvant therapy that is only administered after surgery.

- Once all the necessary pathology and staging reports are available to support clinical decision-making, neoadjuvant therapy must be initiated without delay. Ideally, there should be no more than 4–6 weeks between the first meeting with the patient and initiation of treatment (III.A).
- Neoadjuvant therapy is indicated at and above cT2 AND cN0 OR c/pN-positive status (including occult breast cancer). Neoadjuvant chemotherapy is recommended for all tumours larger than 2 cm in size where chemotherapy is otherwise indicated, and especially for TN and HER2-positive subtypes (I.B).
- During treatment, physical examination before each cycle and, if necessary, imaging check-ups of the patient at least after the second cycle are recommended, and placement of clip markers is required before treatment in cases in which there is a potential for breast-conserving surgery.
- If the primary unresectable tumour demonstrates regression in response to chemotherapy and/or chemotherapy plus biological therapy, completion of all the planned chemotherapy cycles before surgery is recommended (I.B).
- If the primary unresectable tumour does not show adequate remission, a change in the chemotherapy protocol or radiation therapy is recommended to achieve resectability.
- In case of progression or suspected progression, surgery should be performed if possible (except for inflammatory breast cancer, see below).

- When the breast cancer is resectable, the timing of chemotherapy (whether pre- or postoperative) does not influence the long-term disease course (II.C). For primary resectable cases, inadequate remission or even progression after the first 3 to 4 cycles indicates the need for surgery.
- If distant metastases are detected during neoadjuvant (primary systemic) treatment, the patient should be treated according to the recommendations given for metastatic breast cancer.
- Following successful surgery, the previously initiated treatment should be continued, with adjuvant systemic therapy as described below:
  - If the patient was not administered the entire course of preoperative chemotherapy, then completion of the previously (prior to surgery) successful combinations is recommended, or
  - If the patient finished the entire course of the planned neoadjuvant chemotherapy, then—outside of a clinical trial—further chemotherapy is contraindicated even in the absence of pCR. Exception is the TN and HER2+ patient group where in the case of residual tumour (not pCR) administration of 6–8 cycles of capecitabine in TNBC (50) (I.C) or in HER2-positive cases administration of T-DM1 (58) is justified (I.C).
- If an unresectable Stage III breast cancer cannot be made resectable even with neoadjuvant chemotherapy (±anti-HER2 ± endocrine therapy), further treatment must be defined on an individual basis (radiation therapy, chemotherapy, endocrine therapy) (V.C).
- Addition of a platinum derivative (usually carboplatin) to the usual treatment increases the likelihood of pCR in cases of TN breast cancer (I.C).
- Adjuvant administration of Olaparib for 1 year after completion of local treatment and (neo)adjuvant chemotherapy in high risk tumors significantly prolongs IDFS and DDFS in patients with germline BRCA1/2 mutations based on the results of OlympiA study (OS results are awaited) (66).
- Preferred adjuvant and neoadjuvant chemotherapy treatments for HER2-negative cases):
  - Dose-dense AC (doxorubicin, cyclophosphamide) every 2 weeks, 4×, then paclitaxel every 2 weeks, 4×
  - Dose-dense AC every 2 weeks, 4×, then weekly paclitaxel 12×
  - TC every 21 days, 4–6× (docetaxel—cyclophosphamide) (recommended only as adjuvant therapy in Russia)
  - Dose-dense AC/EC (epirubicin, cyclophosphamide) every 2 weeks
  - AC every 3 weeks, 4×, then paclitaxel weekly, 12×
  - AC every 21 days, 4×, then docetaxel every 21 days 4×
  - EC every 21 days, 8× (in selected cases; in some countries only 4–6 cycle are allowed by regulation).
  - TAC/TEC every 21 days, 6× (docetaxel, doxorubicin/epirubicin, cyclophosphamide) (not recommended in some countries; generally not preferable).
  - CMF every 28 days, 6× (in selected cases; recommended only as adjuvant therapy in certain countries).

Primary Systemic Endocrine Therapy

- Neoadjuvant endocrine therapy can be used for tumours demonstrating strong HR expression. Since ER-positive/HER2-negative carcinomas, especially the lobular and luminal A-like subtype, are generally less sensitive to chemotherapy, endocrine therapy is expected to provide greater benefit.
- Sensitivity to the therapy can be predicted based on characteristics such as low grade, occasionally a special histological type (e.g. mucinous, tubular carcinoma), low Ki67 expression, high ER and PR expression, HER2-negativity, and slow progression. Similarly, a low OncotypeDX® score is a predictor of good hormone sensitivity.
- Frequently, due to the general condition and age of the patient the physician is forced to administer primary ET for HR-positive tumours even in the absence of other signs of marked hormone sensitivity, and occasionally—unless followed by surgery—this primary ET remains the definitive therapy (V.C).
- For postmenopausal women the recommended length of primary ET before surgery is at least 6–8 months. If there is good response to the neoadjuvant ET, which is generally administered for 4–8 months or until maximal tumour response, then the therapy should be continued after surgery (I.A). If no regression can be detected after 2–4 months, a decision must be made whether to continue neoadjuvant therapy.
- When choosing neoadjuvant ET, the same rules must be followed as for adjuvant treatments.
- In premenopause, neoadjuvant endocrine therapy is not routinely recommended outside of clinical trials, although in selected luminal A-like tumours endocrine therapy (LHRH + AI) can be given as primary systemic therapy when the patient is not suitable for optimal surgery.
- Following surgery the proven, effective treatment is then continued as adjuvant therapy for 5–10 years. The postoperative treatment may be adjusted based on the histology of the surgical specimen, the extent of regression, the PEPI score (67), and phenotypical changes in the tumour.

PRIMARY SYSTEMIC TREATMENT OF INFLAMMATORY BREAST CANCER (T4D)

From the clinical standpoint, the primary objective of the treatment of inflammatory breast cancer is to transform a primary unresectable tumour into a resectable one. Achieving maximal remission requires the use of the most effective treatment since minimal response or stable disease means that the tumour remains unresectable.

Recommendation

- During evaluation/staging bilateral breast and lymph node assessments, imaging studies of the breast with MRI, PET/CT (or CT), and photographic documentation are recommended.
- The particulars of PST are identical to the medications and protocols used for the neoadjuvant therapy of non-inflammatory breast cancers (see above).
  - Sequential anthracycline-taxane combination is also the preferred treatment in this case and should be supplemented with trastuzumab and pertuzumab if the tumour is HER2-positive.
- The international expert committee primarily recommends a dose-dense chemotherapy regimen (AC, followed by paclitaxel, plus primary GCSF prophylaxis) (68, 69), but when taking into account cardiac toxicity the EC regimen is also considered to be acceptable.
- Multidisciplinary treatment of inflammatory breast cancer may include primary radiation therapy in addition to PST.
- Following successful PST, modified radical mastectomy, axillary dissection (I.B) and post-mastectomy irradiation (II) are recommended even for patients with complete response.
- Institution of adjuvant after-treatment based on prognostic and predictive factors is recommended, as described in the chapter on neoadjuvant therapy.

POSTOPERATIVE SYSTEMIC TREATMENT OF LOCALLY RECURRENT, RESECTABLE BREAST CANCER

A local recurrence is predictive of a high risk of metastasis and/or additional local recurrences, and therefore administration of systemic therapy (chemotherapy and/or hormone therapy) and, if possible, radiation therapy should always be considered in such cases.

- Based on a small trial (the CALOR trial) (70) chemotherapy is only likely to provide a benefit if the tumour was HR-negative (the extent and biological properties of the primary tumour are not relevant in this case).
- The following factors must be considered when choosing a systemic treatment:
  - The biological characteristics of the resected tumour specimen (biopsy) (the receptor assays must be repeated!)
  - Previously used protocol(s) and administered doses
  - Time elapsed between the primary tumour and recurrence
  - General condition, comorbidities, organ reserves, and preferences of the patient (V.A)
- Notes:
  - Use of osteoclast inhibitors in early breast cancer is discussed later.
  - The use of CDK4/6-inhibitors are investigated also in (neo)adjuvant setting. No clear recommendation can be given, in the MonarchE trial abemaciclib combined with ET demonstrated a significant improvement in IDFS in patients with HR+, HER2-node-positive EBC at high risk of early recurrence (71, 72).
  - Adding immunotherapy (PD-1/PD-L1 inhibitor) to chemotherapy in triple-negative tumours is an issue. In the phase 2 GeparNuevo trial additional durvalumab improved long term outcome (iDFS, DDFS, OS) (73). In the phase 3 KEYNOTE-522 trial additional pembrolizumab improved EFS irrespective of PD-L1 status (74).

Recommendation

- Hormone therapy and, if possible, radiation therapy should always be considered
- Chemotherapy is only likely to provide a benefit if the tumour was HR-negative

SYSTEMIC TREATMENT OF LOCALLY ADVANCED (UNRESECTABLE) AND DISTANT METASTATIC BREAST CANCER (STAGE IV)

Criteria for Choosing Systemic Treatments

- Metastatic breast cancer is usually incurable, but with carefully chosen treatments good response and maintenance of stable disease with minimal/acceptable side-effects can yield long-term survival. The objectives of palliative therapy are alleviation of symptoms, improvement of the patient's quality of life, and the extension of life expectancy (V.A).
- Metastatic breast cancer is primarily treated with systemic therapy and/or radiation therapy, and surgery is performed only in a small fraction of cases with stable oligometastatic disease.
  - Palliative surgery and radiation therapy can be considered for brain metastases, meningeal-spinal cord compression, pleural, pericardial, biliary duct, or ureter obstruction, pathological or imminent pathological bone fractures, and localized painful bone or soft tissue metastases, while for liver metastases or cutaneous metastases on the chest wall, regional intra-arterial chemotherapy can be considered in individual cases and carefully selected patients[§].
- Systemic treatment is chosen according to the following factors:
  - The biological behaviour of the tumour.
  - The extent of the tumour.
  - The general condition and biological age of the patient.
  - Comorbidities, possible drug interactions, previous treatments, disease-free interval, and patient preference.
- Chronological age (for elderly patients) or over-treatment (in the case of young patients) is not an acceptable reason to avoid treatment (I.E).
- The recommendation is to perform a biopsy of the metastasis or metastases whenever is approachable and possible to determine prognostic and predictive factors,

primarily at the time of appearance of the first metastasis (I.B).[3]
  - Biopsy can be omitted if it has no therapeutic consequences, cannot be carried out due to the general condition of the patient, or is not feasible for technical reasons. If a biopsy cannot be performed, a liquid biopsy may be an alternative option if available (e.g., for PI3K mutation status).
  - It should be kept in mind that lesions assumed to be metastases may in fact hide a second primary tumour, which is another reason to support biopsy.
  - If the pathological characteristics of the primary tumour and the metastasis are different, there are no clear rules as to which lesion should guide treatment. In such cases the specimens should be compared and re-evaluated. The choice of treatment should be primarily based on the latest pathology report (V.B).
- The biological characteristics of the tumour are key determinants of palliative pharmacological therapy. Endocrine therapy is recommended for most HR-positive and HER2-negative tumours (see section on *Endocrine Therapy*). The exceptions are cases where visceral crisis is diagnosed and when hormonal resistance is suspected or proven. A visceral crisis is not the equivalent of visceral metastasis; rather, it is a major organ dysfunction characterized by rapid progression of symptoms and complaints, laboratory abnormalities, and the disease. Visceral crisis is present if the metastasis leads to the rapidly progressing decrease of organ functions (most frequently liver failure, respiratory failure, bone marrow failure, leptomeningeal infiltration etc.) (4). This is a situation where effective therapy is indicated in a narrow time frame, particularly because if the efficacy of the treatment is inadequate, further treatment is not feasible due to progression and the consequent worsening of the patient's general condition. Apart from a few outliers, chemotherapy is the basis of treatment for HR-negative and HER2-positive (HR + or HR−) diseases. Chemotherapy should be supplemented with targeted therapy following biomarker studies.

Endocrine Therapy for Metastatic Breast Cancer

- Endocrine-based therapy (ET) is the recommended primary treatment option for HR-positive and HER2-negative disease even in the presence of visceral metastases, except for visceral crisis or primary endocrine resistance (I.A). Primary endocrine resistance is present if the previous endocrine therapy/therapies was/were ineffective (see below).
- Molecular targeted agents (CDK4/6 inhibitors, everolimus and PIK3CA inhibitors) are parts of standard ET (if available); preferably as early-line treatments matched to the sequence and effects of prior therapies.
- Treatment is administered continuously until progression, and toxicity is usually not a limiting factor. Sooner or later hormone resistance can develop, necessitating a change in therapy, which is usually one of the next line of agents if the prior agent produces a good response.

The choice of endocrine treatment is influenced by prior therapies:

- The choice of first-line ET depends on the type and duration of adjuvant ET as well as the time elapsed since the completion of adjuvant ET.
- They may include AI, TAM, and fulvestrant, with the addition of ovarian ablation/suppression (medicinal or surgical) for pre- and perimenopausal women (I.A). In pre- and perimenopause, laparoscopic bilateral oophorectomy provides hormone depletion (as well as birth control) and helps avoiding tumour flare reaction caused by LHRH agonists (I.C)

Recommendations for endocrine therapies—in premenopause patients with HR+ mBC

- In addition to ovarian ablation/suppression with an appropriate agent (LHRH analogue or oophorectomy) the postmenopause algorithm should be followed with or without targeted therapy (I.A). In premenopausal status the basis of first-line ET is therefore ovarian ablation/suppression (I.A). For patients refusing ovarian ablation/suppression, tamoxifen monotherapy can be administered as optional ET although this method is less effective (I.D).
- Targeted molecular agents increase the efficacy of conventional ET and significantly impact on the overall survival of the patients. As metastatic first-line therapy, combination of CDK4/6 inhibitors with non-steroidal aromatase inhibitor (NSAI) significantly improved median PFS and OS in MONALEESA-7 trial (75, 76).

Recommendations for Endocrine Therapies—In Postmenopause Patients With HR+ mBC

As first-choice treatment for metastatic disease, combination of CDK4/6 inhibitors with NSAI significantly improved median PFS (24–25 months) in all clinical trials [PALOMA-2 (77), MONALEESA-2 (78, 79), MONARCH-3 (80)] with acceptable side-effects for (non-NSAI-resistant, see below) patients who had not received prior ET or progressed after previous adjuvant therapy. OS benefit was also proven in the "first-line" MONALEESA-2 trial. Therefore, this is the first-choice therapy recommended for postmenopausal patients (supplemented with ovarian ablation/suppression in pre- and perimenopause, NCCN category 1), and for men (supplemented

[3]According to the health care financing rules currently in force, after adjuvant therapy with trastuzumab the administration of the same agent in metastatic cancer requires measurement of HER2 overexpression, while measurement of HER2 overexpression must be carried out for lapatinib therapy.

with an LHRH agonist based on the MONALEESA-3 trial). In cases of NSAI resistance, this therapy should be combined with fulvestrant in the first line (PALOMA-3 (81, 82), MONALEESA-3 (83-85), MONARCH-2 (86, 87) trials). There is no data on continued treatment with CDK4/6 inhibitor after progression, therefore its use is not recommended beyond progression.

Recommended Combinations

- NSAI (anastrozole, letrozole) + CDK4/6 inhibitor (abemaciclib, palbociclib, ribociclib) (I.A).
- Fulvestrant + CDK4/6 inhibitor. The benefit of first-choice fulvestrant is confirmed for endocrine therapy naive patients with only bone metastasis (88) (II.B). For patients who were only given ET as first-line treatment, the combination of CDK4/6 inhibitor + fulvestrant resulted in a median PFS extension of 5–7.5 months (9.5–20.5 months) and improved quality of life [abemaciclib (89), palbociclib (90), ribociclib (85)]. This combination showed an OS benefit in the MONALEESA-3 trial (91, 92) (ribociclib) for postmenopausal patients, and in the MONARCH-2 trial (93) in both pre-/perimenopause and postmenopause (abemaciclib) (I.A).
- In the event of progression after combination NSAI + CDK4/6 inhibitor treatment, fulvestrant is considered standard therapy (94).
- Everolimus + exemestan:
  - Progressed during or within 12 months after completion of adjuvant treatment, OR.
  - For patients who progressed during or within 1 month after completion of treatment of advanced disease (91,95).
  - Supplemented with LHRH for male patients[§].
  - In pre- or perimenopause, in addition to ovarian ablation/suppression since it significantly extends PFS but provides no OS benefit (I. B).
  - However, side-effects associated with combination treatment should be taken into consideration for this treatment (I.B). Tamoxifen (96) and fulvestrant (97) can also be combined with everolimus[§] (II.B).
  - The benefit of everolimus administered after CDK4/6 inhibitor is currently unknown.
- Fulvestrant 500 mg + anastrozole (II.B) (98).
- Endocrine monotherapy:
  - NSAI (anastrozole, letrozole) (NCCN category 1).
  - SAI (steroid aromatase inactivator; exemestan).
  - Selective ER down-regulator SERD (fulvestrant 500 mg) (NCCN category 1).
  - Selective ER down-modulator SERM (tamoxifen).
- Abemaciclib as monotherapy—after prior ET and CT[§] (99) (III.C).
- In case of known PIK3CA mutation (exon 9 or 20) after AI, (approved in Europe only after AI monotherapy) fulvestrant + alpelisib[§] (100) (I.B)].
- As a third or subsequent choice, a treatment not previously used can be considered:
  - Tamoxifen
  - The choice of ET is influenced by prior treatment: if progression was detected during or <12 months after NSAI therapy used as adjuvant endocrine therapy, no good therapeutic effect can be expected (acquired resistance), and the next line fulvestrant should be chosen. Finally, in subsequent lines the following medications can be considered: tamoxifen or possibly exemestan.
  - Gestagens (megestrol acetate and medroxyprogesterone acetate).
  - Low-dose oestrogen (a few studies were published on its use after the development of endocrine resistance).
  - Insufficient evidence is available on re-challenge with certain previously used and effective agent, but it can be tried (IV.C).

Currently there are no known predictive biomarkers for the selection of patients for whom targeted therapies (CD4/6 inhibitors and mTOR inhibitor) would be beneficial and of the best choice among these therapies. Therefore, after considering the known side-effects, these therapies can be used for the treatment of all patients without exception if they are in line with the criteria described in the summary of product characteristics and visceral crisis is not present (I.E). There is no data available for the scenario of progression during CDK4/6 inhibitor treatment and successful switching to a different CDK4/6 inhibitor treatment, or whether switching ET would be beneficial clinically. Similarly, in the case of progression during everolimus therapy there is no evidence that everolimus would be effective when used in a different combination (NCCN category 1).

- Concomitant administration of chemotherapy and ET does not demonstrate any survival benefit, and therefore this combination is not recommended outside of a clinical trial (II.D).
- Chemotherapy followed by continuing treatment with maintenance ET is the logical next step in preserving the benefits of treatment, but data from randomized trials are not available at this point (II.B). Maintenance treatment after chemotherapy with ET plus CDK4/6 inhibitors is not recommended (ABC5).

The Definition of Hormone Resistance (According to ABC5)

The choice of endocrine therapy is influenced by prior treatment: if progression was detected during or <12 months after NSAI therapy used as adjuvant endocrine therapy, no good therapeutic effect can be expected (acquired resistance), and the next line fulvestrant should be chosen (I.A).

Primary Endocrine Resistance

- Relapse during adjuvant ET (within the first 2 years).
- Progression developed during the first 6 months of first-line ET for metastatic disease.

Secondary Endocrine Resistance

- Relapse after ≥2 years during adjuvant ET.
- Progression within 1 year of completed adjuvant ET.
- Progression during ET used for >6 months in advanced disease, or progression within 1 month of completion of ET due to any cause.

For the treatment of HER2-positive and HR-positive advanced breast cancers, concomitant administration of a hormone inhibitor and an anti-HER2 agent is recommended after completion of chemotherapy. If chemotherapy cannot be administered, the first choice for metastatic disease is NSAI + trastuzumab (101), although recently the addition of pertuzumab is also recommended (II.B), and the combination of letrozole + lapatinib (102, 103) is approved for treatment in postmenopause.

Chemotherapy in Metastatic Breast Cancer

General Considerations

- In the presence of a rapidly progressing tumour causing significant symptoms (visceral crisis) administration of combined chemotherapy should be considered, otherwise sequentially administered monotherapies are recommended, as these haven similar survival results and significantly lower toxicity (I.A).
- In metastatic disease, anthracyclines and taxanes are the most effective chemotherapy agents and are therefore recommended if they have not been used before. Reinduction of these agents should be considered if at least 1 year has elapsed since perioperative treatment (in the case of anthracyclines, the cumulative dose must be considered) (I.B).
- Additional recommended medicinal products: cyclophosphamide, capecitabine, vinorelbine, gemcitabine, carboplatin, sacituzumab govitecan or possibly cisplatin, and eribulin (see the recommended chemotherapy combinations) (I.A)(3).
- The duration of the recommended combination treatments is not defined: this depends on such factors as treatment efficacy, side-effects, and patient's preferences. In general, therapy should be continued until progression or intolerable side-effects. The judgement of the patient must be included when defining tolerability (I.B) (2).
- Metronomic treatment refers to daily low-dose oral administration [cyclophosphamide + methotrexate (104), capecitabine + vinorelbine (105), capecitabine monotherapy (106)]. It is primarily recommended for the treatment of tumours with less aggressive biological characteristics. No comparison with standard treatments was performed (I.B).
- Addition of bevacizumab to first line therapy extends PFS but has no effect on overall survival. There is no known biomarker. Only selected patients can receive it as first-line treatment, in cases where other targeted treatments are not available (e.g., PD-L1 negative triple-negative cancer) and potential side-effects must also be considered. The best results were obtained with paclitaxel (107) (I.C).
- Based on the available results of a Phase 3 trial, the administration of platinum derivatives are primarily recommended for patients with a detectable germline BRCA pathological mutation (108) (I.B). Platinum-containing treatment should be considered for patients with a known BRCA mutation (II.B).
- The combination of CT with immunotherapy is an option in PD-L1 positive triple-negative breast cancer (see later).

Recommendations

- In the presence of a rapidly progressing tumour causing significant symptoms (visceral crisis) administration of combined chemotherapy should be considered, otherwise sequentially administered monotherapies are recommended (I.A).
- Anthracyclines and taxanes are the most effective chemotherapy agents and are therefore recommended if they have not been used before. Additional recommended medicinal products: cyclophosphamide, capecitabine, vinorelbine, gemcitabine, carboplatin, sacituzumab govitecan or possibly cisplatin, and eribulin.
- Metronomic treatment is primarily recommended for the treatment of tumours with less aggressive biological characteristics (II.B).
- Addition of bevacizumab to first line therapy extends PFS but has no effect on overall survival (I.B).
- The administration of platinum derivatives are primarily recommended for patients with a detectable germline BRCA pathological mutation (II.B).

Systemic Treatment of HER2-Positive Advanced Breast Cancer (Locally Advanced, Stage IV or Recurrent Breast Cancer)

- For patients with HER2-positive recurrent/stage IV breast cancer anti-HER2 targeted therapy in combination with chemotherapy should be offered as first-line therapy in the absence of contraindications (I.A).
- Patients progressing on a HER2-targeted therapy should be offered additional subsequent treatment with a HER2-targeted therapy since continuous suppression of the HER2 pathway is beneficial (I.A).
- The choice of the HER2-targeted therapy will depend on previously administered therapy, relapse-free interval, patients' preference and country-specific availability (V.C).
- The optimal sequence of available HER2-targeted therapies for recurrent/stage IV is currently not defined and relies on clinical experience (V.C).
- The optimal duration of HER2-targeted therapies is currently not known. The HER2-targeted therapy should be continued until progression or unacceptable toxicity (V.C).
- In patients achieving a complete remission, the optimal duration of maintaining HER2-targeted therapy is not known. Continuing HER2-targeted therapy until progression or unacceptable toxicity is recommended. Stopping HER2-targeted therapy after several years of sustained complete remission may be considered in some

patients, particularly if treatment rechallenge is available in case of progression (V.C).
- For patients with HER2-positive/HR-positive recurrent or stage IV breast cancer, for whom the combination of HER2-targeted therapy and chemotherapy was given as first-line therapy, it is reasonable to use endocrine therapy in combination with HER2-targeted therapy as maintenance therapy after stopping chemotherapy, although this strategy currently has no supporting data from randomized clinical trials (V.C).
- HER2-targeted therapy and anthracyclines should not be given concurrently outside of a clinical trial (V.D).

First-Line Therapy

- The preferred first-line option is pertuzumab plus trastuzumab in combination with chemotherapy. The combination of dual HER2-targeted and chemotherapy has proven to be more effective than the trastuzumab plus chemotherapy in terms of overall survival in this population. The preferred chemotherapy is docetaxel (I.A), or paclitaxel (I.B) (109, 110). Following the induction period with chemotherapy (at least six cycles/ 18 weeks of treatment), a maintenance therapy is recommended with the continuation of dual HER2-blockade, and the addition of endocrine treatment if ER-positive (II.A).
- For patients previously treated in the neo- and adjuvant setting with anti-HER2 therapy, the combination of chemotherapy and dual HER2-targeted therapy (trastuzumab plus pertuzumab) is an important option for first line therapy. (I.A) However, in the Cleopatra trial neo- and adjuvant trastuzumab was administered in only 10% of the patients and all of these had a trastuzumab free interval for more than 12 months (4).
- Currently there are no evidence supporting the continuation of dual HER2 blockade with trastuzumab and pertuzumab beyond progression, with the switch of the chemotherapy agent after progression. Therefore, dual HER2 blockade should not be given beyond progression (4) (V.C).
- When pertuzumab is not available, first-line regimens can include trastuzumab combined with a taxane or vinorelbine (111). Other alternative options are the combinations of trastuzumab and chemotherapy [such as trastuzumab + paclitaxel + carboplatin (109, 112), trastuzumab + capecitabine (113, 114). (III.C).
- First line options for HER2-positive/HR-positive disease include treatment with a HER2-targeted therapy plus chemotherapy or endocrine therapy. Chemotherapy combined with HER2-targeted therapy is still the optimal regimen for HER2+/HR + recurrent or stage IV cancer. However, endocrine therapy in combination with HER2-targeted therapy, such as trastuzumab and pertuzumab in combination with endocrine therapy is being a less toxic approach compared with HER2-targeted therapy plus chemotherapy (115, 116) (II.A). The approach of endocrine therapy plus a HER2-targeted agent should be reserved for highly selected patients, including those with contraindications to chemotherapy, patients with a strong preference against chemotherapy or those with a long disease-free interval (DFI), minimal disease burden and/ or strong ER/progesterone receptor (PgR) expression (4). Combination regimens of HER2-targeted therapy plus endocrine therapy include the combination of an aromatase inhibitor ± trastuzumab, aromatase inhibitor ± lapatinib, or aromatase inhibitor + lapatinib + trastuzumab (117, 118).
- In case of patients progressing after the completion of adjuvant trastuzumab or trastuzumab plus pertuzumab therapy for early-stage disease, the choice of therapy depends on the interval that has elapsed since the completion of the HER2 inhibitor therapy. For patients with a DFI of 6–12 months after the completion of the adjuvant or neoadjuvant therapy trastuzumab and pertuzumab in combination with chemotherapy can be recommended. (II.B) For patient with an interval of less than 6 months between completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer T-DM1 therapy is the preferred first-line systemic therapy. (I.A) A combination of lapatinib + capecitabine is also an option (4, 119, 120) (I.C).

Second-Line Trastuzumab-Based Therapy

- T-DM1 should be preferred in patients who have progressed after first-line, trastuzumab-based therapy. T-DM1 as a second-line therapy has been proven to be more effective compared to lapatinib + capecitabine, and provides an overall survival (OS) benefit (121). According to the results of DESTINY-Breast03 study trastuzumab-deruxtecan is more efficient than T-DM1 in second line setting and it may the preferred second line option in the future (122) (I.A).

Third-Line and Beyond Therapy

- The therapeutic options for later lines of therapy depend on the patient's preferences, toxicities developed during earlier therapies, and the availability of therapeutic agents.
- For patients who have progressed on T-DM1 or trastuzumab-containing therapy, the combination of trastuzumab plus lapatinib or lapatinib plus capecitabine is a reasonable option (119, 120, 123-127). (I.C) Only limited clinical data are available on the use of the combination after pertuzumab or T-DM1.
- Tucatinib plus trastuzumab in combination with capecitabine showed benefits in terms of median PFS and OS in comparison with trastuzumab plus capecitabine in patients who have progressed on trastuzumab, pertuzumab, and TDM1 including patients with brain metastases (128, 129). Tucatinib plus trastuzumab and capecitabine could be considered in third- and later line of therapy (I.A).
- Trastuzumab deruxtecan showed effectiveness in heavily pretreated patients with HER2-positive advanced breast cancer, and is a valid option in this setting (130) (III.A).
- The combination of neratinib plus capecitabine was compared with lapatinib plus capecitabine as third line

or beyond therapy, showing a minimal benefit in PFS, and with no significant difference in OS (131) (I.C).
- Margetuximab plus chemotherapy showed only a small PFS benefit of 1 month when compared with trastuzumab plus chemotherapy in patients pretreated with trastuzumab, pertuzumab and T-DM1 (132) (I.B).
- Currently the new HER2 targeted agents, such as tucatinib, trastuzumab deruxtecan, neratinib, and margetuximab should be recommended for third and later lines of therapy.
- For later lines of therapy trastuzumab can be administered with several chemotherapeutic agents, such as: taxanes, vinorelbine, capecitabine, platinums, and eribulin (III.A).

Recommendation

- For patients with HER2-positive reccurent/stage IV breast cancer anti-HER2 targeted therapy in combination with chemotherapy should be offered as first-line therapy in the absence of contraindications (I.A).
- Patients progressing on a HER2-targeted therapy should be offered additional subsequent treatment and the HER2-targeted therapy should be continued until progression or unacceptable toxicity (I.A).
- It is reasonable to use endocrine therapy in combination with HER2-targeted therapy as maintenance therapy after stopping chemotherapy (III.B).
- HER2-targeted therapy and anthracyclines should not be given concurrently.
- The preferred first-line option is pertuzumab plus trastuzumab in combination with chemotherapy (I.A).
- Dual HER2 blockade should not be given beyond progression.
- When pertuzumab is not available, first-line regimens can include trastuzumab combined with a taxane or vinorelbine (I.A).
- The approach of endocrine therapy plus a HER2-targeted agent should be reserved for highly selected patients.
- T-DM1 should be preferred in patients who have progressed after first-line, trastuzumab-based therapy (I.A).
- Possible treatments for patients who have progressed on T-DM1 or trastuzumab-containing therapy: combination of trastuzumab plus lapatinib or chemotherapy not used before, lapatinib plus capecitabine, tucatinib in combination with trastuzumab and capecitabine, trastuzumab deruxtecan.

Immunotherapy in Metastatic Breast Cancer

- Breast cancers are not among the highly immunogenic tumours.
- PD-1/PD-L1 inhibitors administered as monotherapy have demonstrated low efficacy.
- Combinations of these agents with chemotherapy have been studied in Phase 3 clinical trials.
  - In the KEYNOTE-119 trial, second or third line pembrolizumab given to patients with TN metastatic breast cancer did not provide overall survival benefit compared to chemotherapy given as monotherapy (133).
  - In the IMpassion130 trial (134), TN patients were treated with first-line nab-paclitaxel plus atezolizumab or placebo. The significant PFS benefit that was detected did not translate into OS benefit in the entire study population (135) (II.A).
  - Impassion131 trial failed to demonstrate any advantage (nor PFS or OS) in TN metastatic breast cancer when atezolizumab was added to paclitaxel (136) (II.A).
  - In the KEYNOTE-355 trial pembrolizumab added to chemotherapy (taxane or gemcitabine-carboplatin) the OS gain was clinically meaningful and statistically significant in PD-L1 positive tumours (CPS ≥ 10) (137) (I.A).
- Based on the results, determination of PD-L1 status is recommended for patients with irresectable, locally advanced, or metastatic TN breast cancer. A combination of pembrolizumab plus chemotherapy (taxane or gemcitabine-carboplatin) with CPS ≥ 10 or atezolizumab plus nab-paclitaxel with PD-L1 expression ≥1% is recommended as first-line therapy for these patients.

Recommendation

- Determination of PD-L1 status is recommended for patients with irresectable, locally advanced, or metastatic TN breast cancer.
- For patients with PD-L1 expression and no previous chemotherapy for their metastatic disease, a combination of atezolizumab and nab-paclitaxel (PD-L1 IC ≥ 1%) or pembrolizumab added to chemotherapy (taxane or gemcitabine-carboplatin, PD-L1 CPS ≥10%) is recommended (I.A).

SUPPORTIVE AND PALLIATIVE THERAPY

Pharmacological Management of Bone Metastases

Among the metastases that emerge during the progression of breast cancer, bone metastases—detected in more than half of all cases—are the most common. Bisphosphonate therapy is the essential palliative treatment used in such cases.

- Administration of bisphosphonates (pamidronate, clodronate, zoledronate, or ibandronate) is recommended for bone metastases if,
  - The patient's life expectancy is at least 3 months and the renal function is acceptable (creatinine clearance ≥30 ml/min). During bisphosphonate therapy, the patient's renal function must be checked with the frequency defined in the SmPC (zoledronic acid: before each treatment, ibandronic acid: every 3 months) The current dose must be chosen in line with current renal function values.

- Periodic measurement of electrolyte levels (calcium, magnesium, and phosphorus) is recommended, in parallel with imaging studies.
- Appropriate vitamin D3 (400 IU/day) and calcium (500 mg/day) supplementation is required to prevent hypocalcaemia. The best option is to rely on albumin corrected calcium values.
- Compared to pamidronate, zoledronic acid decreases the risk of sequelae of skeletal system events (pathological fracture, transection, necessity of bone irradiation or surgery) by 20% and its short infusion period is much more comfortable for patients.
- Oral ibandronate is less effective in decreasing the risk of skeletal-related events but induces a marked lengthening of the interval before the first skeletal-related event.
- Zoledronic acid therapy administered every 3 months[§] can be considered the equivalent of the standard monthly therapy (I.B). An optional regimen is the administration of intravenous bisphosphonate therapy once a month at the beginning, and later the frequency can be reduced to once every 3 months (V.C).

- An additional therapeutic option for bone metastases is inhibition of the RANK (receptor activator of nuclear kappa-B) ligand.
  - Denosumab has been found to be more effective in the prevention of skeletal-related events than zoledronic acid.
  - Compared to bisphosphonates its administration (in the form of subcutaneous injection) is more comfortable for the patient, especially if the patient is not receiving other intravenous agents.
  - Denosumab can be used for the treatment of patients with severe renal impairment. The risk of hypocalcaemia is elevated under these conditions.
- The recommendation is to begin treatment with zoledronic acid or denosumab regardless of whether symptoms are present. Both medications are suitable for combinations with other anti-tumour medicines. In many countries, denosumab is approved for the treatment of progression detected during bisphosphonate therapy. However, denosumab was statistically superior to zoledronate in delaying both the first and subsequent skeletal related events and delayed worsening of bone pain (138).
- While the summary of product characteristics specifies that zoledronic acid (ibandronic acid, pamidronate, etc.) dosage should be adjusted according to the creatinine clearance values, the rules applied to denosumab therapy are less strict. A worsening of renal impairment is accompanied by an increase in the risk of hypocalcaemia as well as an increase in parathyroid hormone levels. It is therefore especially important to check the calcium levels of these patients regularly.
- The physician must consider the fact that regular bisphosphonate treatment is accompanied by a risk of developing osteonecrosis of the jaw. Bisphosphonate and denosumab therapy should be preceded by a dental consultation, and any intervention affecting the jaw as well as oral hygiene treatments such as dental cleaning, restorations, and treatment of mucosal inflammation. Appropriate vitamin D and calcium supplementation are also recommended to prevent hypocalcaemia (see above).
- In the presence of malignant hypercalcaemia, intravenous administration of bisphosphonate therapy is the proper approach.

Among adjuvant therapies affecting bone metabolism, the adjuvant use of bisphosphonates[§] in patients in postmenopause improves disease-free survival and metastasis-free survival, and decreases the incidence of bone metastases and overall survival (139) (I.A). This effect is not seen in premenopause but it is present in both the HR-positive and HR-negative patient groups, i.e., it is not exclusively connected with endocrine therapy. A similar effect on survival could not be confirmed in the case of denosumab in early breast cancer, therefore this medication is not recommended associated with endocrine therapy (140, 141).

- In the presence of low oestrogen levels, breast cancer therapy recommended to be supplemented with bisphosphonates (e.g., zoledronic acid, oral clodronate or ibandronic acid every 6 months) (142), especially in high-risk disease (I.A)[§]. It is also recommended if the patient develops osteoporosis (I.A).
- During endocrine therapy, regular bone density measurements and, depending on the results, substitution are recommended in women receiving either an AI or OFS and men on ADT for >6 months with either a BMD T score of <2 or with two risk factors for fracture (I.A).
- Denosumab 60 mg every 6 months is the treatment of choice to prevent fractures in men on ADT and postmenopausal women with early breast cancer at low risk for disease recurrence (I.B).
- Weight-bearing exercise, smoking cessation, reduced alcohol intake and vitamin D supplements (and calcium) should be encouraged (I.B) (138).

Recommendation

- Administration of bisphosphonates (pamidronate, clodronate, zoledronate, or ibandronate) or denosumab is recommended for bone metastases and for malignant hypercalcemia (I.A).
- Periodic measurement of electrolyte levels (calcium, magnesium, and phosphorus) is recommended, in parallel with imaging studies.
- In the adjuvant setting and in presence of low oestrogen levels, breast cancer therapy recommended to be supplemented with bisphosphonates, especially in high-risk disease (I.A).

SYSTEMIC TREATMENT OF SPECIAL SUBGROUPS

Systemic Treatment of Hereditary Breast Cancer

In hereditary breast cancer based on germ cell mutation of the BRCA gene, the accepted guidelines for adjuvant systemic therapy

are essentially identical to those applicable to non-hereditary (sporadic) breast cancers of identical immunophenotype, while there are several additional BRCA-specific treatment options for metastatic cases. Most breast cancers caused by germ cell BRCA (most frequently BRCA1) mutation are triple-negative. Based on gene expression studies, these are basal type cancers but likely represent a separate group. BRCA2-mutant tumours are typically luminal B-like. The genome of BRCA-associated tumours becomes unstable due to tumour suppressor gene errors and deficient DNA-repair mechanisms.

- Tumours originating from these errors are more sensitive to DNA-damaging cytostatic agents, mainly to those that lead to DNA cross-linking, such as platinum derivatives.
- The activity of platinum derivatives has been proven in both retrospective and randomized neoadjuvant trials. According to the results from multiple trials, pathological complete response of above 60% could be verified (143).
- The use of PARP inhibitors (olaparib, talazoparib) developed to inhibit PARP repair mechanisms provides PFS benefit compared to standard chemotherapy (144) (I.B).
- In the OlimpiA phase 3 adjuvant trial 1 year of olaparib added to standard adjuvant therapy in patients with gBRCA mutation and high-risk tumour (those with no pCR and CPS + EG score of ≥3) yielded a significant improvement in iDFS and DDFS. OS data are immature (145).

Recommendation

- Adjuvant/neoadjuvant treatment of patients is based on risk stratification. Accordingly, in cases of moderate-to high-risk triple-negative breast cancer the standard recommended systemic adjuvant treatment is the anthracycline-taxane sequence (AC-docetaxel or AC-paclitaxel); adjuvant platinum-containing therapy cannot be recommended due to a lack of sufficiently significant prospective data. Consider 1-year olaparib after standard (neo)adjuvant chemotherapy in high-risk patients.
- Similar principles are followed in metastatic cases, but also considering the type of previous adjuvant/neoadjuvant treatment, the interval since recurrence, the presence or absence of visceral crisis, etc. Platinum-based products, anthracyclines, taxanes and methylating agents are beneficial chemotherapies for HR-negative and HR-positive cases alike. The standard endocrine therapy algorithm can be used in hormone-sensitive cases. These treatment options can be supplemented with PARP inhibitors suitable for both HR-negative and HR-positive subgroups (143, 146-148). The optimal order of the sequence has not yet been established, but it is known that their efficacy is decreased by recent prior platinum therapy or clear resistance to platinum-containing agents. The latest ESO-ESMO international consensus provides level I. c evidence for the recommendation of platinum-based therapy for metastatic BRCA-associated triple-negative or hormone-resistant breast cancer if the patient has received prior anthracycline (with or without taxane), or PARP-inhibitor, or if the patient has received prior anthracycline (with or without taxane), and endocrine therapy for the luminal type.

For both early and advanced disease participation in clinical trial is recommended.

Systemic Treatment of Male Breast Cancer

Male breast cancer is a rare disease; its incidence is 1:100 that of female breast cancer. Due to the low incidence of the disease, there are no separate therapeutic recommendations, therefore it is assumed that—since generally male patients could not be included in trials—the principles of treatment are like those used for female patients. However, increasing amounts of data support the hypothesis that male breast cancer and female breast cancer are separate diseases (149-156).

The incidence of the BRCA1 mutation is 1%–5% among male patients, and of the BRCA2 mutations 5%–10%, and the presence of the mutation indicates worse prognosis (149). It is important to bear in mind during follow-up that the BRCA mutation makes the patient susceptible to prostate cancer and pancreatic cancer.

Recommendation

- During systemic therapy for early-stage cancer (neo) adjuvant chemotherapy should be chosen according to the treatment principles used for female breast cancer. For HER2-positive tumours 1 year of trastuzumab therapy is recommended, just like for women (IV).
- Most male breast cancers are hormone-sensitive, and therefore endocrine therapy is one of the essential parts of adjuvant treatment. The standard therapy is still 5 years of adjuvant tamoxifen, but based on positive data from the ATLAS trial (157) 5 + 5 years extension can be used in high-risk cases. In addition to tamoxifen therapy, it is very important to support adequate compliance, because according to data in the published literature compliance is lower among male patients, which can potentially lead to treatment failure.
- The preferred endocrine agent is tamoxifen. Use of an aromatase inhibitor can be considered if the patient is unable to tolerate tamoxifen, but it must be combined with an LHRH analogue.
- The principles governing systemic therapy of advanced metastatic disease are identical for men and women.
  - If the tumour is hormone-sensitive, endocrine therapy is the first choice, and an additional endocrine therapy sequence can be administered in case of progression. However, the evidence for these treatments is significantly weaker than it is for women.
    - Traditionally the standard first-choice medicine is tamoxifen, with an expected response rate of over 80%.
    - If there is disease progression during tamoxifen treatment or if tamoxifen is contraindicated for a different reason, then endocrine therapies used for the treatment of female breast cancer are administered, and aromatase inhibitors are to be combined with an LHRH analogue (or orchiectomy).
    - The most recent (2019) guidelines from the ABC5 consensus conference (4) included the recommendation of standard therapy consisting of endocrine therapy

combined with CDK4/6 inhibitor (aromatase inhibitor or fulvestrant) as first or second-line therapy for male metastatic breast cancer, in the absence of visceral crisis, and in combination with LHRH analogue.[§] This is currently considered an off-label treatment in many countries and requires approval from both the national drug and health care and financing authorities.
  - If there are ongoing clinical trials, male patients should be encouraged to join.
  - Endocrine therapy should be continued until the tumour becomes endocrine resistant or visceral crises develop.
  - Second- and third-line treatments after CDK 4/6 inhibitor combination can be similar as in women (extrapolation of results) or reinduction of tamoxifen is possible, depending on previous treatments.
  - Options for endocrine therapy in later lines include aminoglutethimide, androgens, corticosteroids, and LHRH analogue therapy.
- As in female breast cancer, the presence of visceral crisis or endocrine resistance of HR-negative disease necessitates the use of chemotherapy. The treatment principles are identical for female and male breast cancers.
- Similarly, the recommendation for HER2-positive breast cancer is the use of HER2 inhibitor combination according to the same principles as for female patients.
- There are very limited clinical data on the use of mTOR and PARP inhibitors, but the principles are identical to those applied for female patients[§] (V.C) (156).

Systemic Treatment of Occult Breast Cancer

Occult breast cancer may present in the form of axillary lymph node metastasis (this is the most common form) or in rare cases in the form of other distant metastases (in abdominal organs and lymph nodes, omental infiltration, etc.). The latter cases are more characteristic of lobular breast cancer, and, like axillary metastatic carcinoma of undetectable breast cancer, the primary tumour cannot be detected in the breasts even with detailed examinations. The recommended treatment for these cases is metastatic protocol based on immunophenotype.

Recommendation

- The treatment of cases manifesting as isolated axillary lymph node metastases is identical to that of locoregional or locoregionally advanced disease.
- Endocrine therapy is recommended in the presence of high ER/PR levels and low proliferation rate.
- Chemotherapy is recommended in the case of visceral crisis.
- Verified HER2 positivity requires HER2 inhibitor treatment using the same rules as described above.

Breast Cancer During Pregnancy and Lactation

Malignant diseases diagnosed during pregnancy are rare, accounting for approximately 0.02%–0.1% of all pregnancies. Nevertheless, as women increasingly delay pregnancy the incidence of malignant tumours is expected to increase. Breast cancer during pregnancy accounts for 3% of all cases, amounting to approximately one case per 3,000 pregnancies.

Diagnosis

Due to physiological hyperplasia during pregnancy, the breast parenchyma becomes more solid and nodular on palpation, making physical examination more difficult. Tumours are typically diagnosed in the form of palpable nodules with several months' delay. The pregnancy-associated breast cancer is considered to have a poorer prognosis even when controlled for stage and hormone receptor status (158).

Ultrasonography is the primary tool for the evaluation of breast complaints in pregnant women. If necessary (e.g., suspected tumour, DCIS/EIC component, etc.) mammography can be performed, observing radiation protection guidelines. Breast MRI is more difficult due to the necessity for contrast material, as well as the increased abdominal circumference and prone position during the scan. Generally, the administration of MRI contrast medium during pregnancy is a relative contraindication, can be applied "if the clinical status of the woman necessitates it" (the label of contrast media should be checked before use). There are major differences between contrast media and their uses in different countries, therefore the summary of product characteristics should be followed in all cases. Ultrasound is a safe method for staging and shielded X-ray may be used. CT scan and bone scintigraphy are contraindicated.

To determine the pathological diagnosis a core biopsy should be performed, since its sensitivity is approximately 90%. In all cases the pathologist must be informed of the patient's pregnancy.

Treatment

The treatment should be based on the disease stage (159).

- Breast cancer during pregnancy requires continuous monitoring of the patient by the gynaecologist. Pre-term delivery should be avoided if possible.
- Systemic treatment:
  - Breast cancer therapy can be administered during pregnancy, after first trimester, and termination of the pregnancy by itself does not improve the prognosis.
  - During the first trimester chemotherapy is contraindicated.
  - During the second and third trimesters chemotherapy can be administered.
  - Starting at the second trimester all chemotherapy treatments must be preceded by antenatal consultation and fetal monitoring is recommended.
  - After week 35 (or at least 3 weeks before the expected delivery date) chemotherapy is not recommended to avoid delivery complications caused by pancytopenia.
  - The largest body of experience is with the combination of doxorubicin/epirubicin and cyclophosphamide.
  - There is less experience with the use of taxanes; if clinically indicated, a weekly regimen of paclitaxel can be recommended during the second and third trimesters.

- Anti-HER2 therapy and hormone therapy are contraindicated during pregnancy.
- The response to chemotherapy must be quantified, and the condition of the fetus must be monitored regularly before each anthracycline-containing treatment or every 3–5 weeks when administering local taxane treatment.
- Monitoring of tumour response is performed according to daily routine after 3–4 cycles of anthracycline or 12 weeks of taxane therapy, but control studies can be performed at shorter intervals if clinically justified.
- If no tumour response is detected, the oncology team should revise its opinion accordingly. Results from the patient's antenatal monitoring should be present to determine further actions.
- Breastfeeding is not recommended during chemotherapy.
- Safe anti-emetic agents include ondansetron, lorazepam and dexamethasone.
- Corticosteroids are not contraindicated, prednisolone may be safer in the first and second trimester (160).
- G-CSF can be safely used.

- Surgery can be performed in any trimester. According to American recommendations breast surgery can be performed after week 25, but an obstetrician and a perinatal specialist must be available and ready to intervene in case of early delivery (161).
  - It should be taken into consideration for choosing the type of surgery (mastectomy or breast-conserving operation) that radiotherapy is possible only after delivery. If radiation therapy can be delayed until after the delivery, breast-conserving surgery is not inferior to mastectomy.
  - Appropriate axillary staging is a required part of surgery. If the axilla is clinically negative, sentinel lymph node biopsy can be performed.
  - According to the latest recommendations, primary reconstruction is accepted after mastectomy.
- Radiation therapy is contraindicated during pregnancy.

Treatment of Phyllodes Tumour

- The primary treatment is surgery.
- Neither adjuvant endocrine therapy nor adjuvant chemotherapy provide any confirmed benefits. In rare cases of systemic progression, systemic treatment according to the soft tissue sarcoma protocol is recommended.

DISCUSSION

This recommendation reflects the content of the main international guidelines. However, there are minor differences between these guidelines, and the members of the board have chosen the one that best suits their regional circumstances. It may deviate from one or other of the international guidelines in this regard and may give rise to further discussions. The manuscript was completed in February 2022 and does not contain the scientific results published thereafter. The authors are convinced that the discussion leading to the drafting of this manuscript and the guideline itself represent a significant advance in the care of breast cancer patients in the Central and Eastern European region.

This is part 2 of a series of 6 publications on the 1st Central-Eastern European Professional Consensus Statements on Breast Cancer covering imaging diagnosis and screening, pathological diagnosis, surgical treatment, systemic treatment (present paper), radiotherapy of the disease and related follow-up, rehabilitation and psycho-oncological issues.

AUTHOR'S NOTE

The consensus document contains product placement without the intention of advertising. Each complex molecular test is unique, and although these can be described without indicating their name (for example with the number of genes tested), not everyone will necessarily understand what this refers to. For this reason, and adopting the practice used in some of the source works, the tests are listed under their trade name.

AUTHOR CONTRIBUTIONS

The original manuscript was written by GR, JK, ZH, ZK, MD, MK, BP, EK, and KB. The manuscript has been revised and updated by all the authors listed above and NC, DK, BK, BM, and IB-S. The final version of the manuscript has been approved by all authors.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

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Breast Cancer Survivorship Programme: Follow-Up, Rehabilitation, Psychosocial Oncology Care. 1st Central-Eastern European Professional Consensus Statement on Breast Cancer

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Follow-up includes ongoing contact with and health education of the patient, surveillance and control of the adverse effects of surgery, oncological therapies or radiotherapy, screening of metachronous cancers, and comprehensive (physical, psychological and social) patient rehabilitation, which may be enhanced by a healthy lifestyle. Primary attention should be paid to early detection and, when needed, curative treatment of local/regional tumour recurrences. Similarly, with the hope of curative solution, it is important to recognize the entity of a low-mass and relatively indolent recurrence or metastasis (oligometastasis); however, there is still no need to investigate distant metastases by routine diagnostic imaging or assess tumour markers. Below there is a list of possible sources of support, with respect to adjuvant hormone therapy continued during long-term care, social support resources, pivotal points and professional opportunities for physical and mental rehabilitation. Individual solutions for specific issues (breast cancer risk/genetic mutation, pregnancy) are provided by constantly widening options. Ideally, a complex breast cancer survivorship programme is practised by a specially trained expert supported by a cooperative team of oncologists, surgeons, breast radiologists, social workers, physiotherapists, psycho-oncologists and psychiatrists. The approach of follow-up should be comprehensive and holistic.

Keywords: follow-up, healthy lifestyle, physical rehabilitation, psychosocial oncology care, social rehabilitation, side-effect management

INTRODUCTION

The recommendations below are based on the available literature in English and the authors' own experience, and they are in line with comprehensive national and international recommendations on the topic published in English (1–3).

The document constitutes one of a series of guidelines developed by the consensus development panel method (4). Within a complex breast cancer survivorship programme follow-up care restricted to patients considered healed and various types of supportive and palliative measures that should start already at the diagnosis of breast cancer and should be practised throughout its management if needed will be reviewed.

Since all consensuses based on clinical practice and the current literature, this consensus will need to be updated as the field evolves. Panel members agree that as a future advancement, a dietitian, a self-help group leader and a GP expert will be involved in the update of this document.

FOLLOW-UP CARE

Follow-up care means the regular check-up and support of breast cancer patients who are clinically tumour-free, usually have undergone breast surgery, and many of them need adjuvant hormone therapy (1–3). Follow-up care tasks:

- Communication with the patient, facilitating adherence to adjuvant treatment, coordination of care and rehabilitation.
- Health education, lifestyle advice (healthy diet, physical activity, etc.).
- Detection of relapse, rapid and effective assessment if relapse is suspected.
- Facilitating and supporting toleration of adjuvant hormone therapy.
- Detection, prevention and treatment of consequences of the disease and side-effects of surgical and adjuvant treatments (referral to mental, physical and social rehabilitation services, if needed).
- Tertiary screening: prevention and early detection of metachronous cancers (this is usually the same as the screening strategy for the average risk population; in individuals with BRCA mutations, breast screening, possibly gynaecological screening, and gynaecology assessment during tamoxifen therapy, annually or with individually determined frequency, is recommended).
- Declaration of the patient's health status or need of treatments.
- Special aspects: genetic risk, pregnancy.

The atmosphere of long-term care differs from that in active oncology treatment facilities: patients should be empowered to return to their normal life and restore their health; they should be provided with help for full rehabilitation. Patients' independence should be reassured, but at the same time they should be provided with a sense of security, support, and background for the disease they have overcome. During long-term care, the patients should receive adequate information about their situation, state of health and the procedures involved, so that they can fit it into their lifestyle; in the event of a relapse, quick and effective help should be provided to resolve the situation. All these require individualized, open communication, providing a sense of care, and an atmosphere of trust (4, 5). It may also be necessary to involve the patient's family members and close relatives. Currently in Hungary, long-term care is provided by oncologists, but in many countries there is an effort to assign long-term care tasks to GPs or nurses. This requires training and protocols, as well as proper communication with the treatment team. Some of these tasks are highlighted below.

Health Education, Lifestyle Advice (Diet, Physical Activity, etc.)

The most important aspect is making efforts to achieve healthy body weight, since primarily overweight, but also increased BMI have been associated with an unfavourable prognosis. Although the relation between cancer-related outcome and body weight or diet could not be demonstrated, these factors may adversely affect overall health (including anticancer therapy-related adverse effects), secondary cancer incidence and all-cause mortality rates. Optimal body weight is based on a healthy diet (high in fruits, vegetables, and whole grains and low in processed foods or added sugars) and a right amount of exercise that is not contraindicated even after breast surgery (see *Physical Rehabilitation*, also). It is recommended that patients stop drinking alcohol and quit smoking (1–3, 6, 7). For all these, thorough patient educational activity is needed or, in special cases the help of a registered dietitian.

Detection of Relapse, Assessment of Suspected Relapse

When examining a patient, it is essential to keep in mind their individual risk for local/regional recurrence or metastasis. The risk of relapse depends not only on the primary tumour status, but also on the treatment administered. If the patient does not receive adjuvant therapy despite a high risk of recurrence, the vigilance of both the treating physician and the patient is essential, the latter being achieved by providing the patient with adequate information. Breast cancer subtype should also be considered: hormone receptor-negative and rapidly proliferating tumours may recur within 5 years after the first treatment, while the risk of relapse for hormone receptor-positive tumours remains constant for at least 10 years.

Long-term care is based on careful (purposeful) medical history and physical examination. Instrumental investigations for the assessment of systemic relapse (e.g., diagnostic imaging of the chest, abdomen, bones, tumour marker tests) are only required if there is an indicative complaint or symptom. Indeed, intensive assessment in asymptomatic cases will not affect either the time of diagnosis of metastasis or survival, but it may compromise quality of life due to anxiety and addiction. By contrast, diagnostic imaging of the operated breast and regional lymph nodes requires great care: after breast-conserving surgery,

TABLE 1 | Adverse consequences of breast cancer treatments complained during follow-up.

Treatment	Side effects developing during treatment	Side effects developing months or years after treatment
Surgery	Numbness, body image problems, cosmetic outcome, sexual dysfunction, restricted motion of the shoulders, pain	Lymphoedema, neuropathy, restricted motion of the shoulders, pain
Radiotherapy	Skin lesions, breast fibrosis, asymmetry, cosmetic issues, pain, body image disorders, sexual dysfunction, pneumonitis, lymphoedema	Soft tissue fibrosis, ischaemic heart disease, radiogenic secondary malignancy
Chemotherapy	Cognitive impairment ("chemo brain"), fatigue, early menopause, infertility, sexual dysfunction, hair loss, weight changes, neuropathy, cardiomyopathy	Sterility / hormone deficiency / menopause, osteoporosis / osteopenia, leukaemia / myelodysplastic syndrome, cardiomyopathy
Trastuzumab	Reversible heart damage	
Tamoxifen	Hot flushes, menstrual disorders, mood disorders, vaginal discharge/ infection, elevated triglyceride levels	Stroke, endometrial cancer, thromboembolic event, osteopenia in premenopause
Aromatase inhibitors	Vaginal dryness, decreased libido, joint and muscle pain, increased cholesterol levels, gastrointestinal symptoms, urinary incontinence, impaired cognitive functions	Osteoporosis, risk of fracture

both the operated and contralateral breast should be assessed on a yearly basis, as recommended by a breast radiologist, usually via mammography and ultrasound or MRI (see the chapter on Breast Diagnostics) (1–3). For lobular carcinoma, it is particularly important that ultrasound scanning be part of a complex diagnostic imaging follow-up even after 5 years (3).

The diagnosis of an oligometastatic condition, which has been identified in recent years as a new biological entity, is of paramount importance (8). Radical local treatment of a slowly progressing and low-mass tumour can be life-saving in some cases. Therefore, if it is suspected, it should be rapidly confirmed with sensitive testing methods, with the hope of a curative treatment and favourable therapeutic outcome (9, 10).

In some cases (e.g., when they cannot present for long-term care due to a comorbidity), patients may be managed by a GP who would follow the recommended protocol. It is important to inform patients about the course of the follow-up care and the abnormalities that may occur due to the disease or the treatment.

Detection, Prevention and Treatment of Consequences of the Disease and Side-effects of Surgical and Adjuvant Treatments (Support, Rehabilitation)

Expected side-effects and abnormalities depend on the type of treatment administered, the dose and duration of treatment, the patient's age and comorbidities. Possible consequences of different treatments are shown in **Table 1** (1–3, 11–19). Side-effects can lead to temporary or long-term decline in body image, physical condition and ability, and mental status, all of which will compromise quality of life (18).

Due to changes in body image, various tools (wigs, breast prostheses, etc.) and breast reconstruction may be considered as immediate or delayed solutions. Complex treatment of the issue is recommended (physical and mental help).

Lymphoedema should be prevented by losing weight if the patient is overweighted and by protecting the arm (physical activity is allowed, but weight-bearing by the arm should be avoided, efforts should be made to prevent erysipelas, but venous access to the arm or blood pressure measurement on the operated side is not contraindicated, moreover it may even cause anxiety if it were prohibited (14).

Monitoring of cardiotoxic consequences should be continuous during active oncology treatment; during long-term care, special cardio-oncology care is needed for patients at risk (pre-existing heart disease, prior oncological treatment with cardiotoxic drugs or cardiac/coronary artery radiation exposure), or if there are symptoms suggesting cardiac disease (breathlessness, fatigue, cardiac decompensation) (15,16).

Monitoring bone health and osteoporosis should depend on age and the treatments administered. In case of chemotherapy-induced menopause or endocrine therapy, a baseline DEXA test should be performed and then monitored depending on the treatment (**Table 2**). For joint complaints, rheumatology examination is recommended and physiotherapy may be deliberately used (11). For musculoskeletal complaints caused by aromatase inhibitors, switching to tamoxifen or another aromatase inhibitor may be the solution, if necessary.

Fatigue, mental disorders and cognitive impairment are well-demonstrated as a consequence of chemotherapy, but not fully clarified in the case of hormone therapies (17–21). During long-term care, it is worthy gathering information on this issue and initiating the patient's rehabilitation, if needed.

The use of a lubricating cream or suppository in case of sexual complaints or vaginal dryness may be tried, and medicinal treatment or pelvic floor exercises may be recommended for urinary incontinence (22).

Managing Endocrine Therapy

Adjuvant hormone therapy is usually recommended for a period of 5–10 years, but due to its long duration and successful return of the patient to a normal life, and partly due to possible side-effects, medication adherence is poor in a significant proportion (up to half, according to certain estimates) of patients. Therefore, one of the most important goals of long-term care is to promote good therapy adherence. Ensuring that patients are informed and perform appropriate follow-up tests, as well as side-effect management, will improve results. **Table 2** shows the recommended follow-up assessments for various treatments. Either due to chemotherapy-induced amenorrhoea or due to

TABLE 2 | Follow-up assessments during adjuvant endocrine therapy.

Medication	Premenopause	Menopause
Tamoxifen	DEXA every 2–3 years Yearly gynecology checkup	Yearly gynecology checkup
GnRH/LHRH analogs	DEXA	—
Aromatase inhibitors	DEXA every two years	DEXA every two years

GnRH, gonadotropin releasing-hormone; LHRH, luteinising hormone-releasing hormone; DEXA, Dual Energy X-ray Absorptiometry (bone density measurement).

GnRH analogues, menopausal symptoms may develop in the form of hot flushes, mental instability, sexual complaints (decreased libido, vaginal dryness), which are deteriorated by aromatase inhibitors (22, 23). Aromatase inhibitors may cause androgen-type alopecia, too. Tamoxifen is more likely to induce vaginal discharge and weight gain. Gabapentin, a selective serotonin reuptake enhancer (SSRE) and lifestyle changes may help in reducing hot flushes, while topical treatment may be considered to help sexual complaints, e.g. lubricant, vaginal suppositories, or laser treatment, as a novel opportunity (1–3, 24). Hormone replacement therapy, even the use of oestrogen-containing vaginal creams, is contraindicated. Rheumatological treatments can be administered for joint or muscle pain (especially common with aromatase inhibitors).

Special Aspects: Genetic Risk, Pregnancy

When a hereditary predisposition to breast cancer is suspected, great caution and tactfulness is required and a sufficiently long time should be allowed for processing the informations (25–27). In cases of a family history suggesting inherited risk of cancer, cancers at a young age, or specific tumour types, testing for BRCA or other hereditary gene mutations is essential and recommended by numerous international guidelines. If justified, and the patient is ready to accept it, the patient may be referred to a genetic counselling centre; ideally this is done at the time of the initial care. If a pathological gene mutation carrier status is confirmed, this has a number of consequences for the follow-up care: preventive breast surgery or adnexectomy depending on future family plans (the risk-reducing effect of Fallopian tube removal with preserving the ovaries is being evaluated in a clinical trial), developing a specific breast screening strategy if needed, or other actions may be considered based on the advice of a geneticist; naturally, the issue of informing and screening the family members also arises.

The issue of undertaking pregnancy depends on the risk of relapse, how this changes over time, and the nature and timing of the administered treatments. During the discussion, it is worthy to understand whether the patient sees her illness in a realistic way and, if necessary, to provide objective information about the situation. There is no evidence that pregnancy *per se* would be detrimental in terms of recovery or recurrence. Chemotherapy may lead to infertility for a shorter or longer period of time; one of the reasons is that hormone production is impaired, although this risk can be reduced by using a GnRH analogue during chemotherapy. The ability to regenerate after chemotherapy and the chance for recovery of fertility decrease with age (28). For infertility, the patient should be referred to a specialist. Due to the genotoxic effects of chemotherapy, a waiting period of at least 3 years is required after chemotherapy. For a successful pregnancy, hormone therapies should be terminated; if the patient received tamoxifen, a latency of 3 months is required before pregnancy, due to the slow clearance of the drug.

REHABILITATION—WITH A HOLISTIC APPROACH

Note the general and official WHO definition for rehabilitation (1980): "Rehabilitation is an organized assistance needed by people with a long-term or permanent damage to their health, physical and/or mental integrity in order to reintegrate into society and their communities. A coordinated, individualized set of medical, pedagogical, social and occupational measures aimed at making the rehabilitated individual a happy and, if possible, a full-fledged citizen of the society. Rehabilitation is a social task."

The original meaning of the word rehabilitation is good news, the restoration of lost honour, satisfaction—within this conceptual framework, the physician or the caring community should assist in restoring the patient's self-esteem and reduce the losses associated with illness (29, 30).

The rehabilitation of a breast cancer patient begins at the time of diagnosis, no matter whether it is an operable/early stage case and has received curative treatment(s), or advanced or metastatic breast cancer that requires continuous treatment and intensive monitoring. Rehabilitation is comprehensive (physical, mental, social) and is conceptually planned; not an *ad hoc* process. Naturally, rehabilitation is tailored to the prognosis of the disease, which can be estimated based on prognostic factors. Altered physical condition and the presence of mental problems are well known issues, and when these appear and are recognized, it is the oncologist's responsibility to refer the patient to a specialist in the appropriate field (physiotherapy, reconstructive surgery, psychosocial oncology care, social worker, etc.). During the follow-up period, the task of the oncologist is to prevent and recognize the symptoms and to refer the patient to an appropriate specialist. For rehabilitation purposes, it would be essential to avoid the stigma of the disease and, while underlining the importance of the investigations, treatments and follow-up, it should be ensured that the disease did not become a central issue of the patient's life, or a determinant of all goals and activities. Comprehensive life counselling is the task of the oncologist that helps the patient's reintegration into the community of the healthy. For effective rehabilitation, it is important to set realistic goals and to take into account the patient's individual physical and mental condition and psychointegrative harmony. A prerequisite for effective rehabilitation is that specialists in the physical, mental and

TABLE 3 | Approximate energy expenditures for selected forms of activities.

Category	Self care	Occupational	Sport	Physical conditioning
Very light MET 3	Bathing, shaving, dish washing, dressing, writing, driving, desk work	Sitting (office) or standing (service) work, truck driving, operating a crane	Playing billiards golf, archery, boating, slow dancing	Walking at 3 km/h, stationary exercise bike with very low resistance, very light gymnastics
Light MET 3–5	Window cleaning, leaf-raking, weeding, sickling, machine mowing, painting, carrying items weighing 7–15 kg	Shelving light objects, light welding, light carpentry, repairing machines, car fixing, hanging pictures, wallpapering	Dancing, golf (walking), sailing, volleyball, doubles tennis, horse riding	Walking at 4.5–6 km/h, cycling at 9–12 km/h, light gymnastics
Moderate MET 5–7	Easy digging, hand grass levelling, slow stair climbing, carrying loads weighing 15–30 kg	Easy carpentry, garbage shovelling, use of pneumatic tools	Badminton, singles tennis, skiing (downhill), light backpacking, basketball, football, ice skating, galloping	Walking at 6.5–7.5 km/h, cycling 9–12 km/h, swimming (breaststroke)
Difficult MET 7–9	Wood sawing, heavy shovelling, stair climbing at limited speeds, carrying loads weighing 30–45 kg	Firing in a furnace, trench digging, pickaxing, shovelling	Canoeing, playing rugby, mountaineering, fencing	Jogging, swimming (freestyle), cycling at 18 km/h, heavy gymnastics, rowing machine workout
Very difficult MET 9	Carrying load on stairs, carrying loads over 45 kg, fast stair climbing, heavy snow shovelling	Wood cutting, hard physical work	Handball, squash, skiing (hiking), intense basketball playing	Running at > 9 km/h, cycling at > 18 km/h or uphill, rope jumping

MET, metabolic equivalent of task.

social spheres, working as a team, are available when necessary, and provide assistance in all aspects of rehabilitation. Within a comprehensive breast cancer survivorship programme various forms of rehabilitation are usually provided at the initiative of the staff who provides care, treatment or follow-up for the patient (29, 30).

The important role of patient advocacy and primary care in the holistic approach should be also emphasized. In fact, breast cancer was the first example for initiating patient advocate activity, and Europa Donna was the first breast cancer advocate group that established a Europe-wide coalition (31). In most countries there are various self-established patient groups that not only provide direct support to patients and their families, but raise social attention, public awareness, reduce stigmatisation and, may have impact on politics too. General practitioners may overtake many breast cancer-specific tasks depending on the need or actual situation such as providing certain tests or delivering certain medications, diagnosing or controlling comorbidities sometimes related to cancer therapy itself, or guiding life style changes etc. In both fields the most important aspect and need is the maintenance of ongoing communication, contact and mutual confidence between the members of the patient advocate group/primary care physician and the representatives of the cancer multidisciplinary expert team.

SOCIAL REHABILITATION

Oncology Social Work

Social work is a supporting activity classified as an applied social science, which promotes social development, improvement of functioning and solving issues at the individual, group and community levels. Hospital social work helps to solve the patients' and their families' social issues. Support can also be requested from the Family Support Institute of the Local Government. Social workers' tasks may include supporting the achievement of social and financial security, mediating individual social services, helping patients back to their home, or guiding patients toward psychosocial oncology care when mood disorders and anxiety are recognized.

Supporting the Social Rehabilitation of Breast Cancer Patients

Social rehabilitation means the process of integration into the community, the criteria of which are the existence of social relationships, relative financial and economic autonomy and the ability to ensure the means of subsistence. Social rehabilitation begins from the moment the diagnosis is established, and continues throughout the treatment period and sometimes the follow-up care period.

Breast cancer is an oncological disease that primarily affects women. The traditional family model of our society has changed, with every second marriage ending in divorce. In many cases, women are breadwinners, and in 86% of single-parent families, it is the mother who raises her children alone. People living in traditional families are also characterized by a "dual-earner" model, so that if the wife/mother falls ill, the family loses earnings (32). This disease brings changes in the lives of those affected and their relatives, and family members need to adapt to this and promote adaptation in others. Limitations of mental and physical stress tolerance, social disadvantages and lack of resources must also be taken into account.

Most Common Social Issues and Their Solutions

In the presence of an oncological disease, patients often cannot keep their jobs due to the treatment, side-effects, and mental strain. It is essential that patients/clients themselves decide whether they feel physically and mentally capable to continue their work (33, 34). If they are unable to perform their job on a

TABLE 4 | Minimum recommended exercise for healthy individuals.

American recommendations	European recommendations
at least 150 minutes/week of moderate intensity or 75 minutes/week of intense aerobic exercise	Minimum 30 minutes of moderate-intensity exercise 5 days a week or at least 20 minutes of vigorous exercise 3 days a week
Exercise should consist of units lasting at least 10 minutes	Activity can be gathered from units of at least 10 minutes
Further beneficial effects result from increasing workout time to 300 minutes/week for moderate-intensity or to 150 minutes/week for vigorous aerobic exercise, in adults. It is recommended to perform moderate or high intensity muscle strengthening activity for 2 or more days, involving all major muscle groups	It is recommended to perform additional muscle strengthening and endurance exercises 2–3 days a week

permanent basis, they may claim insurance and social benefits to compensate the loss of earnings.

We have included the forms of institutionalized social support in Hungary as an illustration in **Supplementary Appendix S1**.

Recognition of the psychological processes and reactions and of depression and anxiety symptoms associated with oncological diseases and treatments contributes to the establishment of patient/client compliance skills and that of a good doctor-patient relationship. The patient's/client's personality and potential coping mechanisms should be taken into account. These are influenced by the patient's values, socialization, attitudes, stress management skills, and also by social factors, workplace and family environment, and whether the patient/client has mental illness or addictions. If depression and anxiety disorders exist or develop, or in the event of need of crisis intervention, the patient/client should be referred to a psychiatrist or psychologist. The patient's/client's mental condition should be monitored since the time of diagnosis, and the help of a specialist should be sought if any change occurs or if a period of the illness may lead to mental vulnerability. It is important that the patient's/client's attitude to mental health would allow the acceptance of the psychological support needed for recovery. Coping with the disease is aided by avoiding isolation and sustaining family, friend, and community relationships. Patients/clients should be guided toward self-help groups and patient organizations, in which they will have the opportunity to share their problems with peers dealing with similar illnesses, who reach out with understanding and set an example of positive vision. After recovery, successful rehabilitation will result in the patient being employed and self-sufficient, which is enabled through employment rehabilitation. Employment rehabilitation means that a previously employed person, who currently has altered work capacity due to illness, is employed in a job matching her current working aptitude. Useful work provides the patient/client with an opportunity to restore self-fulfilment, self-esteem and a sense of worth.

PHYSICAL REHABILITATION

Introduction

According to a WHO survey, sedentary lifestyle is the fourth most important risk factor for current endemic diseases worldwide, including cancer. Physical activity means exercise associated with any muscle contraction involving a change in location or position that requires a higher energy expenditure than at resting level. Isometric and isotonic, eccentric and concentric muscle work can be part of physical activity. Established physiotherapy is an essential part of the complex management of breast cancer all along the disease continuum; since no other chapters of this series deal with physiotherapy, here we summarize the related aspects irrespective of the phase of the disease.

As a result of regular exercise, the organism undergoes structural, functional, and physiological changes that help to prevent and delay many diseases, or recover from them. This effect is also influenced by the form, intensity, duration, and timing of the exercise. To measure the magnitude of the load, we use the term "metabolic equivalent of task (MET)," which is based on measuring oxygen consumption. Knowing the MET value of physical activities, a desired weekly load can be easily established (**Table 3**). Based on the WHO proposal, American and European exercise recommendations were formulated for healthy individuals (**Table 4**).

Physiological Effects of Physical Exercise

- Exercise activates natural killer cells (NK cells) that play a role in killing cancer cells.
- It reduces the body's susceptibility to bacterial infections.
- Supports body weight control.
- Prevents deterioration of cardiorespiratory endurance, which may occur as a side-effect of cardiotoxic antitumour therapies.
- Helps to recover muscle mass, reduces sarcopenia due to disease and treatments.
- Reduces the risk of thromboembolic complications, the incidence of which is 7-fold higher in cancer patients than in the average population.
- Supports correction of abnormal movement patterns, develops the ability to coordinate and maintain balance, which is deteriorated as a common consequence of polyneuropathy caused by chemotherapy.
- Reduces fatigue.
- Reduces symptoms of musculoskeletal syndrome causing bone, muscle, and joint pain and stiffness.
- Increases bone mineral content, which is important for bone loss due to hormone and chemotherapy, and thus reduces the risk of bone fractures.
- Improves self-esteem, reduces the effects of distress, anxiety, fear, pain, and initiates positive self-healing processes.
- Reduces the decline of cognitive functions and slows down the ageing process.
- Reduces the risk of developing lymphoedema.

TABLE 5 | Options of functional locomotory tests.

Function, abnormality	Tool	Manual examination by a physiotherapist
Range of motion (ROM)	Goniometer	functional tests
Muscular strength	Dynamometer	Oxford scale (0–5)
Upper limb volume	optoelectric instrument plethysmography water displacement method Khunke's volume formula	a state characteristic (Khunke's formula) recorded on the basis of a series of circumferences (k1, k2. . .) measured every 4 cm perpendicularly to the axis of the affected limb, suitable for follow-up $\sum V = \frac{K_1^2+K_2^2+K_3^2+K_n^2}{\Pi}$
Scarring, axillary web syndrome, AWS		visible and / or palpable cording pain restricted ROM for flexion and abduction (usually an axillary phenomenon, but elbow and wrist involvement may also occur)

Workout Forms

Aerobic or cardio-training is a continuous or intermittent intense workout of the large skeletal muscle groups for 20–50 min. This type of exercise primarily improves endurance and increases the capacity of the cardiorespiratory system. It includes walking, Nordic walking, running, swimming, cycling, stair climbing, ball sports, etc.

Anaerobic or resistance training is a short-term high level effort that helps to prevent muscle atrophy and osteoporosis. Typical forms of resistance training are weightlifting or sprinting.

Other exercise types, such as breathing gymnastics, proprioceptive training, stretching, etc. can be incorporated into both training types. Different exercise types are not interchangeable, it is the task of a physiotherapist to set an individualized training programme.

The physiotherapist can find out the patient's usual physical activity or fitness *via* a specific questionnaire, such as the IPAQ (International Physical Activity Questionnaire), and can create an individual training plan for the patient based on the FITTA criteria: frequency, intensity, time, type of the exercise and perseverance (approach), and the 5R criteria: Repetitions, Rate, Range, Resistance, and Rest (**Table 5**).

The Place of Physiotherapy in the Perioperative Care of a Breast Cancer Patient

Breast cancer therapy most often begins with surgery, so it is recommended that the physiotherapist be in touch with the oncology team, so that they will be informed about the type of surgery and have the opportunity to meet the patient. It is important that the physiotherapist has a BSc or MSc degree, experience in the field of oncology and a close professional relationship with the surgeon and oncologist (35).

Both the period of preparing the patient for surgery and the early postoperative period impose tasks on the physiotherapist and at the same time affect the patient's later quality of life and the outcome of the disease (36). Early mobilization and physiotherapy will significantly reduce the functional impairment caused by the disease and interventions.

Complex functional impairment of the upper extremities associated with breast surgery may develop including the following:

- Pain, hyperaesthesia, paraesthesia,
- Stiffness,
- Secondary lymphoedema,
- Seroma,
- Scarring (axillary web syndrome, AWS),
- Decreased muscle strength and restricted motion, limited range of motion (ROM),
- Weakening of grip strength of the hand,
- Complex functional impairments,
- Decrease in daily activity,
- Sensory disturbances/losses in the chest area,
- Posture/body image disorder,
- Neck/shoulder girdle dysfunction (involvement of the upper part of the trapezius muscle) (37).

Early and late functional complications of breast cancer treatment along with patient quality of life have long been studied, and a variety of methods are available to manage these in routine patient care (**Table 5**). The possibilities for prevention and treatment will be discussed after a presentation of methodology. Assessing both the range of motion of the shoulder and muscle strength of the upper limb is important. Decrease in grip strength of the hand and a limited range of motion pose serious problems to the patient. Both functional tests and other measuring tools can be used to assess functional restriction, which is also a prognostic indicator (38).

Measurement of the upper limb volume can be performed using several methods, and this will significantly help in the early detection of lymphoedema. Circumference differences measured at six anatomical points are highly correlated with the results of water displacement volume measurement (39).

AWS caused by scarring is a typical group of signs and symptoms following oncological breast surgery. In most of the cases, a scarred cord-like lesion is palpable in the armpit; in a milder form it is only perceived by the patient, and therefore recording subjective symptoms is essential. Predisposing factors, incidence, pathological aspects, and therapeutic options for AWS are being actively researched. The lesion usually develops in the armpit, but it may extend down along the elbow pit to the base of the thumb. The syndrome is caused by the occlusion, inflammation and later on the fibrosis of the superficial lymphatic vessels, as a consequence of surgery (40).

TABLE 6 | Questionnaires designed for complex examination of upper limb functions in patients with locomotor disorders.

"The Disabilities of the Arm, Shoulder and Hand", **DASH**	To measure complex functions of the upper limb	30 questions, of which 25 ask about functions related to lifestyle, and 5 about other symptoms (score 1–5) optional questions related to work, sports, artistic activities (4 for each category)	high score weak function
10 minutes (42, 43) **QUICK DASH**	An abbreviated version of DASH can be evaluated if there are >9 responses	11 questions	high score poor function
3 minutes "Upper Extremity Functional Index", **UEFI**			
3 to 4 minutes (44) **"Functional Assessment of Cancer Therapy", FACT-B** 10 minutes (45, 46)	To measure upper limb function Multidimensional quality of life questionnaire	20 questions (score 0–4) 36 questions (score 0–4)	high score good function high score good quality of life
FACT-B+4 10 minutes (45, 46)	Multidimensional quality of life questionnaire expanded with questions on 4 upper limb functions	40 questions (score 0–4)	high score good quality of life
"Kwan's Arm Problem Scale", **KAPS** 3 to 5 minutes (40)	Upper limb function questionnaire for cancer patients	13 questions (score 1–5) it is also a psychometric indicator pain, stiffness, swelling, function	high score with more symptoms and poor function
"Subjective Perception of Post-Operative Functional Impairment of the Arm", **SPOFIA** 3 minutes	To assess condition after breast cancer surgery	15 questions swelling, pain, anaesthesia, restricted range of motion and decreased muscle strength	a high score indicates marked upper limb damage

The current trend is the global analysis of upper extremity functions that is in addition to the measurement of the range of shoulder motion and anatomical parameters of the upper limb, complex upper limb functions needed to perform everyday tasks, as well as circulatory conditions and physical stress tolerance are assessed (41–45). Questionnaires completed by the patient are also included (**Table 6**).

Preparing the Patient for Surgery

- Assessment of structural and functional condition using the aforementioned tests.
- Evaluation of comorbidities.
- Teaching early mobilization exercises.
- Thrombosis prophylaxis and teaching patients venous exercise and how to use compression bandages.
- Information on the symptoms and prevention of occasional lymphoedema.
- Assessing the need for and use of an aid (optimal prosthesis, bandage etc.).
- Explaining the role of exercise and physical activity in the healing and rehabilitation process.

Early Postoperative Tasks

- Positioning depending on the type of surgery.
- Early mobilization; the goal is to reach a vertical position as soon as possible (sitting, standing, walking).
- Early breathing exercise, chest mobilization to help prevent respiratory complications.
- Vascular physiotherapy or an elastic bandage or anti-thrombosis stocking applied before mobilization reduces the risk of thrombosis.
- Passive, assisted and then active movement of the upper limb on the affected side, teaching facilitation possibilities.
- Prevention of contractures.
- Core stabilization and mobilization.
- Restoring abnormal muscle balance caused by an altered body image.
- Preparing for a complex exercise programme, enrolling the patient in a small group class, as soon as possible.
- After reconstructive surgery (TRAM, LD, DIEP), lifting the arm above 90° have to be avoided for 3–5 weeks.
- Recovery of self-sufficiency functions (measurement of independence based on physical and cognitive capacity according to the "Functional Independence Measure, FIM" scale).

This period lasts for a couple of days, but in case of breast reconstruction surgery it may take longer time. Prior to hospital discharge, patients should be enrolled in a rehabilitation support group, when possible, in which they participate in a regular exercise programme under the guidance of a specialist, preferably a physiotherapist. If this is not available, an exercise programme should be created, which can be performed independently by patients in their home, and sports and other leisure time activities may also be suggested. Since oncology treatments after surgery (radiation and/or chemotherapy, hormone therapy, etc.) are also very demanding on the body, regular physical activity and exercise are essential.

Lymphoedema

Although over the last decade, the widespread adoption of sentinel lymph node biopsy and patient training have significantly reduced the development of upper limb lymphoedema, it is essential that all lymph node-positive breast cancer patients who have undergone surgery, chemotherapy, or radiation therapy are considered potential

lymphoedema patients. Therefore, all interventions and physiotherapy procedures causing significant hyperaemia of the affected upper limb should be avoided. (Harmful effects of blood pressure measurement, blood sampling or possibly intravenous treatment have not been confirmed, but are rather an assumption; regrettably, unjustified fear may cause anxiety in the patient.) Patient information, regular movement therapy, and manual lymph drainage (MLD), if needed, all support the functioning of the lymphatic system possibly damaged by the various oncological interventions, and reduce the probability of the progression of the lymphoedema. Because MLD stimulates lymphatic system activity, treatment should only be initiated with the recommendation of the oncology team since it may even pose a risk to the patient. Lymphatic drainage can be performed by a physiotherapist with specialist knowledge of lymphatic drainage in the field of oncology (46).

Complex lymphatic therapy also includes compression treatment, which may use bandages, stockings, and mechanical compression. It is important to know that use of these measures is not optional.

Compression Elastic Bandage

- Short-elongation, high working pressure elastic bandages are used.
- Applied in multiple layers with pressure decreasing evenly from distally to proximal direction (100%–70%).
- After manual treatment, it should be applied and maintained while the patient is performing active muscle activity.
- This is repeated daily until the reversible mobile part of lymphoedema is removed.

Compression Stockings

- Can be used at 1 to 3 compression gradients.
- Its purpose is to maintain an oedema-free state.
- In some cases it can also be used for preventive purposes.
- The type, size and gradient of stockings should be determined together with the attending physician.
- The stage of lymphoedema and the general condition of the patient and possible comorbidities should also be taken into account.

Machine Compression

- A complementary procedure, it must not be used alone without other anti-oedema therapies.

Early mobilization and active exercise programmes (30–50 min three times per week), complemented with MLD therapy, may significantly reduce the development and progression of the lymphoedema.

Complete decongestive therapy (CDT), which includes both MLD and compression therapy, significantly reduces pain and feeling heaviness in the arm (47).

Conclusion

With their multiple beneficial effects, regular physical activity, sports and leisure activities improve quality of life and life prospects after complex breast cancer treatment. Due to the effects of complex treatment, age-specific characteristics and comorbidities, many of the patients do not know what type of exercise they may or should perform; the help of a physiotherapist is essential. Physiotherapists participate in the complex breast cancer survivorship programme in cooperation with the other specialists, their specific task and responsibility is building, teaching and supervising short-term and long-term exercise programmes. Physiotherapists may be involved in supporting breast cancer patients at the clinic, specialist care, primary care, home care service and in patient organizations all along the disease course according to the actual situation and need. Physiotherapy exercises and other forms of physiotherapy are now a part of integrative oncology and modern comprehensive breast cancer therapy.

PSYCHOSOCIAL LONG-TERM CARE AND REHABILITATION

General Guidelines for Psychosocial Oncology Care

It is now worldwide accepted that psychosocial care and psychosocial rehabilitation of patients diagnosed with breast cancer should be provided as an integral part of complex oncology care (48). This should begin when the diagnosis is communicated to the patient, and be practised within a complex cancer survivorship programme later on.

Relevant recommendations are summarized below, and these explain specific features of care based on general guidelines in psychosocial oncology care (49) and a recent protocol published by the Hungarian Ministry of Health (50). The summary is intended for all the psychologists, clinical psychologists, psychotherapists, psychiatrists, social workers, mental health professionals who work at an oncology centre providing active medical treatment, at an oncology department/outpatient clinic, at a crisis centre for cancer patients and their relatives or in private practice.

Interventions should be adapted to the oncology treatments being given and the patient's current condition, and therefore close collaboration is required between the attending physician and the professional providing psychosocial care, who ideally is a member of the multidisciplinary team (1, 13, 18, 48, 51–63).

A person diagnosed with breast cancer may need psychosocial support and treatment throughout the entire course of the disease (**Table 7**).

The Main Crisis Points May Include

- The period of assessment for the suspected disease.
- Establishment of the diagnosis.
- Preparing for surgery, starting oncological therapy.
- Initiation of oncological therapy, facing the burdens and side-effects of treatment.
- Follow-up/relapse-free period, "recovery to life."
- Relapse, appearancediagnosis of metastases.
- Terminal stage.

TABLE 7 | Common psychosocial symptoms that occur during certain stages of the disease.

Stage of the disease	Possible psychological / psychiatric phenomena and symptoms
Secondary prevention/cancer screening	Anxiety, communication and compliance difficulties, fear of social stigmatization, health anxiety, negligence, fear caused by a positive family history, procrastinating behaviour Psychosocial consequences of confirmed high genetic risk (e.g. insecurity, anxiety disorders, fear of disease)
Diagnostic work-up	Establishment of a doctor-patient relationship and its difficulties; the patient is becoming "familiar" with the health care system, the patient's early experiences are "engraved" and will be decisive; the impact of issues related to the health system on the patient. Fear of "violation" of bodily integrity, fear of pain, fear of the patient role, fear of the loss of autonomy. Temporary narrowing of concentration and thought processes. Frequent intrusion into the private sphere (a matter of trust and attachment!), depersonalization, loss of security, chronic stress (long waiting times, fear of illness)
Communication of diagnosis, preparing for surgical procedures, discussing the treatment	A diagnosis of cancer may often induce psychological trauma, a mental crisis. In addition to the most common fears raised when the diagnosis is communicated (fear of death, loss of autonomy, pain, treatments, etc.), anxiety and depressive disorders (e.g., PTSD), cognitive dysfunction (e.g., restricted thinking and focus of attention), topic-specific problems should be highlighted: body scheme changes, self-esteem, partnership and sexual issues. When a patient first finds out the diagnosis, there may be violent emotional reactions, extreme manifestations, and complete introversion may even occur, which are natural emotional reactions to shock; however, they may require crisis intervention. Information and preparation before the (new) oncotherapy phase reduce anxiety and improve compliance.
Oncotherapy (surgery, chemotherapy, radiation therapy, hormone therapy)	Increasing communication difficulties (between patients, physicians, the medical staff and the relatives of the patient) due to physical and mental stress. Frustration, adjustment difficulties, mental regression, fear of death, internal / external body image disorders, depressive symptoms (due to the loss of health, but may also be biologically or drug-induced or of CNS origin), anxiety, psychosomatic symptoms, PTSD, relationship and sexual problems, psychogenic side effects. Early side effects of chemotherapy, anticipatory nausea and vomiting may lead to treatment discontinuation and prolonged aversion, reducing the possibility of re-treatment in the event of relapse. Unrealistic adherence to or rejection of treatment. Cognitive impairment after chemotherapy: impairment of concentration and integration, learning disabilities (20%–50%), mild decrease in IQ (cognitive impairment may be exacerbated by psychogenic factors). In patients with non-cerebral metastases, mild EEG abnormalities, paraesthesias occur in about 20% of cases. Changes in sexual life, family task allocation, relationship problems. Increasing financial burdens may change the patient's economic and social status. Elevated levels of distress (sleep disturbance, restlessness, mood swings, anxiety, depressed mood, depression, fatigue syndrome), which compromise quality of life. As a result of regular or long-term hospital treatments, hospitalization, separation from the family and social isolation may develop. As a result of increased physical and mental strain, premorbid psychiatric problems may become exacerbated or decompensated; therefore, special attention should be paid to people who have been previously diagnosed or have avoided psychiatry, but are currently suffering from some form of comorbid psychiatric disorder (the importance of screening!). Any treatment type may cause anticipatory anxiety symptoms, grief reactions (due to loss of health or independence, etc.), and anticipatory bereavement.
Follow-up phase/ relapse-free phase	Adaptation difficulties, persistence of conditioned psychogenic side-effects, cognitive impairment, chronic fatigue, Damocles' syndrome, PTSD, sexual disorders, development and exacerbation of addictions; loss of security, psychosomatic symptoms, mood disorders (depression), anxiety disorders (panic disorder, hypochondria, carcinophobia), risk of suicide.
Relapse, palliative care	Emotional crisis, anger, anxiety, depression, fear of death, adjustment / coping difficulties. Increased guilt, emotional instability, tension, anger, overt or hidden hostility, intellectual inhibition, mental regression, depersonalization.
Terminal stage	Fear of death, anxiety; rejection (denial), anger, bargaining, depression, resignation.

TABLE 8 | Algorithm for oncopsychological screening.

Distress → short evaluation (e.g. distress thermometer) + list of problems→	Moderate or severe distress, DT = 4 or more	→	Clinical assessment: validated scales, screening tests to measure anxiety/ depression (oncologist, nurse, social worker or trained professional) in the following cases: • high risk patient ○ high vulnerability period ○ distress risk factors are present-practical issues • family issues • spiritual/religious issues • physical problems • social problems • emotional problems (e.g. anxiety, depression)	→Referral,	→Mental healthcare providers Psychiatry/ psychology care)
→	Non-relieved physical symptoms (treated according to disease-specific or palliative care guidelines)			if needed	→Social worker and counselling services
	Clinically confirmed mild distress or DT <4			Primary oncology care team + available resources	→Spiritual care (pastor)

Source: NCCN Guidelines Version 1. 2020 Distress Management, National Comprehensive Cancer Network (2020) (65).

Important Psychosocial Changes Following the Diagnosis of Cancer

- Emergence of fear of death, dealing with the issue of financial difficulties.
- Changes in body scheme that cause identity confusion (in terms of femininity, motherhood).
- Partnership and sexual problems.
- Difficulties of lifestyle change.
- Financial problems.
- Unbalanced family homeostasis, reversal of roles.
- Uncertainty about the future.
- Fear of recurrence of the disease.

Interventions That Can Be Used Effectively in Mental Care

- Psychoeducation.
- Crisis intervention.
- Psychological counselling.
- Supportive-expressive psychotherapy.
- MBCR (mindfulness-based cancer recovery) programme.
- Relaxation, autogenic training, "imaginative" therapies.
- Other individual and/or group therapeutic techniques, depending on the qualification and skills of the professional providing the care.

For all these, it is essential:

- To assess and be aware of the patient's physical/mental condition (tumour stage, histological type, age, presence of risk factors, level of social support, living conditions, premorbid personality, comorbidities, previous life events, etc.).
- To match psychosocial care carefully and flexibly with oncology treatments.

Recognizing the importance of emotional problems in cancer patients, in 2017 the Hungarian Cancer Society adopted the International Standard of Quality Cancer Care developed by the International Psycho-Oncology Society (IPOS) (57) (https://ipos-society.org/endorsements/organizations):

- ○ Psychosocial cancer care should be recognized as a universal human right
- ○ Quality cancer care must integrate the psychosocial domain into routine care

Distress should be measured as the 6th Vital Sign in addition to temperature, blood pressure, pulse, respiratory rate and pain.

Psycho-Oncological Assessment and Screening Tools

- Quick screening: Distress Thermometer (measures the degree of distress reported by the patient on a scale of 10; above 4, the patient requires support) and Mitchell's Emotional Thermometers (58, 59, 63)
- Mood assessment and recording: BDI, Zung, HADS (56, 60)
- Evaluation of anxiety: STAI, HADS (56, 61, 62)
- Problem List: helps to plan individually tailored support by exploring current psychosocial and spiritual difficulties
- Other psychological measuring instruments, depending on the qualification and competence of the psychosocial or mental health professional
- The basic principle of screening is that screened patients should be provided with psychological care and their psychological assessment should be adjusted to their current physical and mental condition
- All newly presenting patients should be included in oncopsychological screening, regardless of whether they had any premorbid psychiatric illness. It is recommended that tests for quick screening are repeated at different stages of the disease (any treatment event, e.g. relapse; or interim periods, e.g., every six months), preferably in conjunction with oncology follow-up (**Table 8**).

Possibilities for Psychosocial Oncology Care Intervention in Different Phases of the Disease

- Communication of diagnosis: crisis intervention, counselling, supportive therapy, psychodiagnostics, psychosocial screening.
- Initiation of treatment: psychoeducation, reduction of distress, supportive therapies, cognitive and behavioural

therapies, couple therapy, life management counselling, "imaginative" therapies.
- Completion of treatment, recovery: verbal and non-verbal psychotherapies.
- Completion of treatment, deteriorating condition: preventive pastoral care, crisis intervention, support for family members, counselling, supportive psychotherapies.
- Death, dying: dignity therapy, crisis intervention, grieving process embedded in psychotherapy, bereavement support groups, self-help bereavement groups.
- An early preventive approach in interventions is important, anticipating the possibility of recurrence and the effectiveness of second- and third-line treatments, supported by statistical data, if necessary.

- Together with proper communication, this will improve compliance. It will allow for the creation of a long-term therapeutic collaboration plan, the message of which for the patient is that the treating team trusts in their long-term survival and wants to involve the patient in the treatment process.
- Starting from the communication of the diagnosis, during the step-by-step process of information-treatment-preparation, it is recommended that issues relevant in the longer term, such as possibilities of breast reconstruction, or the issue of having children after breast cancer treatment, be addressed gradually.

Professional Conditions for Psychological Support of Cancer Patients

Hungarian National Cancer Control Programme (2006):

- Specialists in the psychosocial treatment of cancer patients (clinical or health psychologist, psychiatrist and/or psychotherapist), working together as members of the oncology team with the oncologist, physiotherapist, dietitian and social worker, should be made available in oncology centres, departments and caregiving services.
- Continuous consultation and documentation between different professions is essential for monitoring changes in the patient's condition.
- The primary goal is to maintain the best possible quality of life and physical well-being while preserving emotional, social and spiritual well-being.
- Appropriate physical environment and work organization, availability of oncopsychological training/further training.

This is part 2 of a series of 6 publications on the 1st Central-Eastern European Professional Consensus Statements on Breast Cancer covering imaging diagnosis and screening (64), pathological diagnosis (65), surgical treatment (66), systemic treatment (67), radiotherapy (68) of the disease and related follow-up, rehabilitation and psychosocial oncology care issues (present paper).

AUTHOR'S NOTE

The consensus document contains product placement without the intention of advertising. Each complex molecular test is unique, and although these can be described without indicating their name (for example with the number of genes tested), not everyone will necessarily understand what this refers to. For this reason, and adopting the practice used in some of the source works, the tests are listed under their trade name.

AUTHOR CONTRIBUTIONS

ZKah and IS have created the section *Follow-Up*, RD created *Social Rehabilitation*, ZKap has created the section *Physical Rehabilitation*, and MM, ZKo and MM have written the *Oncopsychology* section; ZKah has advised reviewed and edited the entire chapter. All the authors participated in the final review and synchronisation of the chapter.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.por-journal.com/articles/10.3389/pore.2022.1610391/full#supplementary-material

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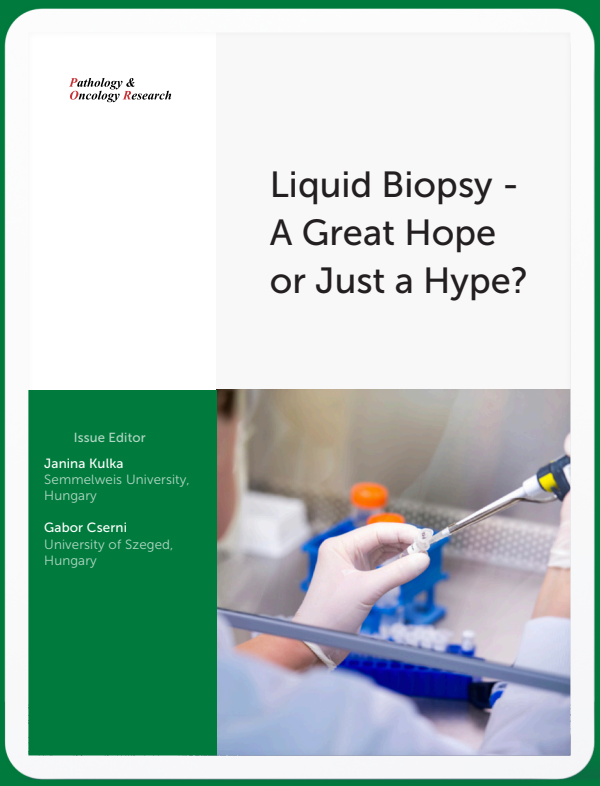

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