Arbeitsgemeinschaft Gynäkologische Onkologie Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2024

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Introduction

Breast cancer is the most frequent cancer in the European Union encountering for >400,000 new cases per year. For women diagnosed with early breast cancer (EBC), the 5-year survival probability is about 96% in Europe [1]. Optimal management of breast cancer requires a multidisciplinary strategy. Each year the interdisciplinary AGO Breast Committee provides updated state-of-the-art recommendations on the prevention, diagnosis and treatment of breast cancer. This update follows a documented algorithm. The most recent and relevant publications are reviewed and the scientific validity is scored according to the Oxford Level of evidence (LoE). The strength of recommendation is determined by the Oxford Grades of recommendation (GR) and the AGO Grades of recommendation. The updated recommendations for EBC and metastatic breast cancer (MBC) of the AGO Breast Committee have been released in March 2024. This paper captures the updated recommendation of EBC. The updated slides with the annotated speeches and the patient forum are available in the on-demand library (https://www.ago.2024.de). Chapters without relevant changes in content are not included in this manuscript.

Options for Primary Prevention and Lifestyle Factors

Options for primary prevention and lifestyle factors primary prevention is defined as preventing disease or injury before it ever occurs. This is done by preventing exposure to hazards that cause specific diseases. Individual risk factors can be classified into nonmodifiable and modifiable lifestyle factors. Currently, there is good evidence that changes in some modifiable risk factors could substantially decrease individual breast cancer risk [2]. Relevant lifestyle factors such as overweight/obesity, physical inactivity, fiber-containing foods, alcohol consumption (LoE 2a/B), smoking (LoE 2a/B), and exposition to ionizing radiation are well known [2]. Adherence to normal body weight (BMI 18.5–25 kg/m^2) as a preventive factor for the development of breast cancer is well investigated, particularly for postmenopausal women (LoE 2a/B/++). For bariatric surgery, there is increasing evidence for a reduction in breast cancer risk [3]. A balanced diet including extra virgin olive oil (LoE 2b/B/

AGO+), nuts (LoE 2b/B/AGO+) (>10 g/die), reduced consumption of fat (LoE 2a/B/AGO+), and reduced consumption of red meat (LoE 2b/C/AGO+) may decrease the incidence of breast cancer [4, 5]. For other factors such as supplementation of vitamin D3 (LoE 1b/B/AGO+/−), vegetarian or vegan diet (LoE 2b/C/AGO+/−), vegetables and fruits (LoE 2a/B/AGO+/−), dairy products or phytoestrogens (LoE 2a/B/AGO+/−), the data are contradictory regarding the reduction of breast cancer incidence. However, it should be considered that prospective randomized trials to investigate the impact of nutrition aspects on breast cancer risk are almost impossible to conduct. In contrast, physical exercise (metabolic equivalents to 3–5 h moderate pace walking per week) has been demonstrated to be efficient in reducing breast cancer risk (LoE 2a/B/AGO++) [6]. Pregnancy related factors (number of full-term pregnancies (LoE 2b/B), first delivery before the age of 30 years (LoE 2b/B), duration of breast feeding (LoE 3a/B) may be preventive for breast cancer, whereas PCO syndrome (LoE 3b/C), assisted reproduction (LoE 2b/B), and abortion (LoE 2b/B) do not influence the risk for EBC [7, 8]. Avoidance of hormone replacement therapy (HRT; especially estrogen/progestin combination regimens) in postmenopausal women may reduce breast cancer risk (LoE 1b/A/AGO+). Oral contraceptives do not increase the probability of death from breast cancer (LoE 1a) [9]. Regarding chemopreventive agents other than endocrine therapy, the effects of 5-Aminosalicylsäure, bisphosphonates, and statins have been evaluated. Some encouraging results suggest that 5-Aminosalicylsäure use might reduce breast cancer risk, particularly regarding hormone receptor (HR) positive or in situ breast tumors and postmenopausal women (LoE 4D/D/+/−). Bisphosphonates are rated (LoE 2b/B/AGO +/−) for primary prevention of breast cancer.

Breast Cancer Risk, Genetics, and Prevention

With regard to genetic testing, the AGO Breast Committee recommends comprehensive counseling based on family and individual history (LoE 2b/B/AGO++) [10], comprising intensive assessment for syndrome-associated breast cancer (non-BRCA; LoE 2b/B/++). Genetic testing for pathogenic variations includes BRCA1/BRCA2 (LoE 1b/A/AGO++), PALB2 (LoE 3a/B/AGO+), CDH, PTEN, TP53, STK11 (LoE 3b/B/AGO+), and ATM, BARD1, CHEK, RAD51C/D (LoE3a/B/AGO+/−) with varying degrees of evidence and impact. Genetic testing of BRCA1/2 germline mutations (gBRCA 1/2mut) is strongly recommended to patients, who are candidates for PARPi therapy in early or metastatic disease [11–13] or in those under 60 years of age with triple-negative breast cancer, irrespective of familiar or individual history [14]. Mutations in BRCA1/2 and PALB2 are associated with an increased lifetime risk for breast cancer of approximately 40%, for ATM, BARD1, CHEK2, RAD51C, and RAD51D, 20–30%, respectively [15]. Genetic counseling for pathogenic mutations of PALB2, as genes with moderate or lower penetrance [16], has to consider risk as continuous rather than categorical variable, influenced by family history, competing risks, and polygenic traits.

Criteria for genetic testing and counseling appear to be broader in the international context compared to Germany (main focus here is established as a population with >10% probability of BRCA1/2 mutations). For example, National Comprehensive Cancer Network (NCCN) guidelines for genetic testing [17] include also patients who are younger than 50 years old (vs. 35 years old cut-of) without family history or testing in all patients with triple-negative BC. Recently published ASCO-Society of Surgical Oncology (SSO) guidelines [18] recommended testing even in all patients who are younger than 65 years old irrespective of family history in addition to NCCN criteria. Testing of significantly more patients leads clearly to lower prevalence of mutations and higher numbers for variants of unclear significance, which will be found. AGO mentions an option for genetic counseling also in these patients (based on physician's/patient's decision and clarification of cost situation).

With estimated high risk for breast cancer, intensified surveillance as well as risk-reducing surgery can be offered. Otherwise an intensified surveillance program include including annual breast magnetic resonance imaging (MRI) should be offered to patients, in particular particularly to those with high-risk mutations. However, without proven genetic risk, risk-reducing surgery should not be offered (LoE 2a/B/−).

Breast Cancer Diagnostics

In asymptomatic women, screening mammography (MG) is highly recommended for women 50–75 years of age (LoE 1a/A/AGO++). In the age of 40–44 years, MG-screening is not recommended (LoE 1b/B/AGO−), so far from 45 to 49 (LoE 1a/A/AGO+) individual shared decision-making is recommended and clear indication is necessary, expanding the Screening age to this age group is actually discussed. Above 75 years of age screening can be offered to women in good health with a life expectancy of 10 years or longer (LoE 4/C/AGO+/−) [19]. Breast density is a known risk factor for breast cancer development and decreased MG sensitivity. Nevertheless, neither use of hand-held ultrasound (US) nor automated whole breast US can be recommended as a sole modality for screening (LoE 3a/C/AGO−) [19]. Using digital breast tomosynthesis, the recall and biopsy rates were low but so

far no general significant reduction in interval cancer rates could be demonstrated (LoE 1a/A/AGO+) [20–23]. Synthetic 2D image reconstruction of the 3D dataset can significantly reduce radiation dose and is highly recommended (LoE 1a/A/AGO++), but the use and availability of the complete dataset for diagnosis and subsequent treatment are mandatory [22, 23]. There is incoming evidence that the use of artificial intelligence as a second reader in MG could be beneficial regarding detection rate and workload optimization, bit still needs further evaluation (LoE 1b/B/AGO+/–) [24].

MRI screening in the extremely dense breast screening group with negative MG showed a significantly reduced interval cancer rate at the cost of slightly increased false-positive cases (LoE 1b/B/AGO+) [25, 26]. For patients with breast symptoms, clinical examination (LoE 3b/B/AGO++), MG (LoE 1b/A/AGO++), digital breast tomosynthesis (LoE 2a/B/AGO+) or contrast-enhanced MG (LoE 2a/B/AGO+), US (LoE 2b/B/AGO++), and minimally invasive biopsies (LoE 1b/A/AGO++) should be performed [27, 28]. As part of surgical planning procedure, ultrasound of the breast (LoE 2b/B/AGO++) and the axilla is recommended (LoE 2a/B/AGO++) [29, 30]. MRI can be helpful for patients with a reduced sensitivity of MG and US, nipple involvement, lobular invasive cancer, suspicion of multicentric disease, and/or high risk (LoE 1b/A/AGO+), provided that MRI-guided vacuum-assisted biopsy access is available in-house or among cooperating partners [27]. Second-look US is recommended in cases of newly detected lesions by MRI. In patients with clinically and/or sonographically suspicious axillary lymph nodes, core needle biopsy is recommended (LoE 2b/B/AGO++). If less than 3 nodes are suspicious or biopsy reveals lymph node involvement prior to neoadjuvant therapy, a clip should be inserted in the lymph node to allow targeted axillary dissection (TAD at the time of surgery. Staging is recommended for candidates scheduled for (neo)adjuvant chemotherapy including CT (chest/abdomen/pelvis) and bone scans (LoE 2b/B/AGO+). PET-CT should be reserved for individual cases with high-stage (III) cancer (LoE 2b/B/AGO +/–) [31].

Pathology

Prediction of endocrine responsiveness is of key importance for clinicians. The pathology report can help as follows:

1. Immunohistochemical detection of estrogen- and progesterone-receptors in paraffin-embedded tissue is a standard procedure. HRs are scored as percentage of positive tumor cell nuclei (estrogen receptor, ER is considered positive if ≥1% with low positivity ranging from ≥1% to 10%; progesterone receptor, PR is considered positive if ≥10% (LOE 1a A, AGO ++) [32].
2. Detection of endocrine responsiveness by Ki-67 decrease to ≤10% in the surgical specimen or a repeat core biopsy after 3–4 weeks of preoperative endocrine therapy in EBC (LOE 1b A, AGO +). This endocrine induction therapy was established by several large phase III trials in >15,000 pre- and postmenopausal patients with HR + HER2- EBC such as POETIC, WSG ADAPT, or WSG ADAPT cycle [33, 34].
3. Detection of secondary, i.e., acquired endocrine resistance by analysis of activating ESR-1 mutations in liquid biopsy or metastatic tissue (LOE 1b A, AGO +). ESR-1 mutations render ER constitually active and thus confer resistance to aromatase inhibitors (AIs). The novel oral SERD elacestrant has been approved in MBC for tumors harboring an ESR-1 mutation [35].

With regard to the indication for checkpoint inhibitor therapy in breast cancer, PD-L1 testing is only needed for the first line setting in metastatic triple-negative setting. Here, a positive PD-L1 immune score (IC) of ≥1% (cytoplasmic staining of the leukocyte stromal infiltrate [lymphocytes, macrophages, plasma cells, granulocytes outside of abscesses] in relation to the tumor area) is needed for therapy with atezolizumab and nab-paclitaxel [36]. For therapy with pembrolizumab and chemotherapy, a Combined Positive Score (CPS, i.e., positive tumor cells + macrophages + lymphocytes divided by the number of tumor cells ×100) of ≥10% is the prerequisite [37]. Testing can be performed in the primary tumor or metastasis tissue (LOE 2 A, AGO ++) using antibodies that are equivalent to those used in the respective registration trials (LOE 3 B, AGO +).

Several next-generation sequencing results with corresponding mutations are a prerequisite for using a targeted therapy in breast cancer: AGO ++ recommendations for testing are Germline gBRCA 1 and 2 for the indication of olaparib in EBC and MBC or talazoparib in MBC; PIK3CA for indication of alpelisib in MBC as well as ESR-1 for elacestrant. Moreover, a somatic BRCA mutation or gPALB2 mutation could also be an evidence-indication for olaparib in MBC (AGO +) as well as an alteration in the AKT1 – PTEN – PIK3CA pathway for an indication for capivasertib according to the recent FDA approval [38].

Prognostic and Predictive Factors

Locoregional tumor burden together with tumor biology (ER, PR, HER2, Ki-67) are the known major prognostic drivers and the key determinants of therapy decisions in EBC. Use of these factors allows definition of patient groups with a low or high-risk profile, and it is important to state that an ER expression between 1 and

9%, defined as ER low, is associated with a loss of ER function and endocrine treatment is not indicated. However, use of adjuvant chemotherapy remains one of the most controversial issues in patients with an intermediate risk (HR+/HER2- BC with 0–3 positive lymph nodes). Gene expression tests like the prospective evaluated Mammaprint® or Oncotype DX RS® tests [39] can help in the decision-making process (LoE 1b/A/AGO+). Additional informations regarding the intrinsic subtypes can be provided with the Blueprint® test, a classifier that comes together with the Mammaprint®. It can be beneficial in neoadjuvant chemotherapy (NACT; LoE 2b/B/AGO +/−) to estimate a better response [40]. Evaluation of endocrine sensitivity by measurement of Ki-67 after 2–4 weeks of preoperative endocrine therapy provides further important information beyond classical clinical and/or genomic prognostic factors (LoE1b/A/AGO+). Results from an exploratory analysis in the ADAPT trial suggest an excellent survival in radial scar (RS) 0–25 and low postendocrine Ki-67 values (≤10%) without chemotherapy use even in premenopausal women [34], whereas a missing Ki-67 drop of <10% is associated with a primary endocrine resistance. Combination of post-endocrine Ki-67 with genomic assays as a treatment decision marker is currently under investigation in the ongoing ADAPTCycle trial, which compares chemotherapy versus endocrine therapy plus ribociclib in patients with HR+/HER2- BC [41]. For HER2-positive disease, the HER2DX test is available to estimate the benefit of trastuzumab +/− pertuzumab (LoE 2b/B/AGO +/−) in the neoadjuvant treatment of HER2-positive disease. The HER2DX pCR-score and risk-score might help identifying the right patient for neoadjuvant dual HER2 blockade in combination with a single taxane [42].

If a chemotherapy is indicated, it is recommended to be performed in a neoadjuvant manner. A poor response to NACT resulting in a non-pCR can be used to indicate post-neoadjuvant treatments. Two scores are able to provide additional and more detailed informations regarding the prognostic meaning of the residual cancer tissue to indicate further treatment, the CPS-EG (LoE 2b/B/AGO +) [43] and the RCB score (LoE 2a/b/AGO+) [44]. Both scores are recommended to be used in daily routine, for example to select HR+/HER2-patients for olaparib after NACT.

Lesions of Uncertain Malignant Potential (B3)

Lesions of uncertain malignant potential (B3) are usually detected by MG or ultrasound and diagnosed by core or vacuum-assisted biopsy in asymptomatic women. Surgical treatment aims to identify potential upstaging to a more severe precursor or even invasive lesions (particularly ductal carcinoma [DCIS]) and to prevent a progression toward malignant disease during follow-up. Atypical ductal hyperplasia (ADH) has a particularly high risk of being associated with in situ or invasive breast cancer [45]. ADH has been treated with an open excision after histopathological confirmation in core-/vacuum needle biopsy (LoE3a/C/AGO++). Open excision may be omitted, if all of the following requirements apply: no mass-lesion radiologically, a small lesion (≤2 TDLU*) in vacuum biopsy, and complete removal of imaging abnormality (LoE5/C/AGO+/−). However, in cases with ADH at margins in open biopsy specimens no further surgery is indicated, if incidental finding accompanies invasive or intraductal carcinoma (LoE 3a/C/AGO+). In cases of biopsy of classical LIN, open excision can be avoided if no discordant imaging, especially no focal lesion is present (LoE 2b/C/++) [46]. In contrast, high-risk variants of lobular neoplasia, which include pleomorphic and florid LCIS (pLCIS and fLCIS) are recommended for open biopsy, and preferably complete excision (LoE 2b/C/AGO++). Flat epithelial atypia is upgraded to DCIS or invasive breast cancer in 5% of all cases. Open biopsy is recommended (LoE 2b/B/AGO +) if vacuum biopsy could not remove ≥90% of the lesion [47]. The diagnosis of solitary or multiple papillomas on core biopsy might be associated with an increased risk of 30% (with atypia) for an invasive carcinoma or DCIS [48]. Therefore, in case of an atypia or multiple lesions an open biopsy is mandatory (LoE 3a/C/++). A RS may mimic carcinoma, mammographically because of its stellate appearance. Radial sclerosing lesions are only rarely associated with atypia or DCIS. When RS is associated with atypia (such as flat epithelial atypia, ADH, or classical LIN), management can be similar to atypia alone [49]. Medical prevention (e.g., low-dose tamoxifen (TAM) (LoE 1b/B/AGO+/−) or AI (LoE 1a/A/AGO+/−) for lesions with uncertain biological behavior may be performed only in very individual cases [50].

Ductal Carcinoma in situ

DCIS is a not life threatening preinvasive lesion that is considered to be a precursor of invasive breast cancer. It represents an extremely heterogeneous group of lesions with variable potential for progression to invasive disease, in which not all DCIS will progress to invasion [51]. Most DCIS cases are detected within the MG-screening. In addition to MG, which is the main diagnostic tool, pretherapeutic assessment in DCIS should also include breast and axillary ultrasound, especially to rule out an accompanying invasive solid part and lymph node involvement (LoE 4/C/AGO++). Breast MRIs might be helpful for assessment of the extension and planning surgical procedure in DCIS (LoE 1a/B/AGO+/−) but can lead to overestimations of the extension of the DCIS and

by that to surgical overtreatment. Complete surgical excision remains the standard of care (LoE 1a/A/AGO++). All guidelines recommend clear margins of 2 mm for DCIS lesions except below the skin and above the muscle. SNLB might be recommended in rare cases if the surgical procedure is not allowing a sentinel lymph node (SLN) in case of an upstaging to invasive cancer (e.g., cases of kind of mastectomy for large DCIS lesions, LoE 3b/B/AGO+). Radiotherapy is commonly recommended after BCS of DCIS (LoE 1a/A/AGO++), whereas systemic endocrine treatment (tamoxifen 20 mg for 5 years or 5 mg for 3 years or anastrozole) is only recommended as an option (LoE1a-b/A-B/AGO+/−) [52]. Independent of DCIS grade adjuvant endocrine treatment AND irradiation have no impact on survival (LoE 1a). Radiotherapy reduces the risk of ipsilateral (invasive and noninvasive) recurrences by 50%. The number needed to treat with radiotherapy (for ipsilateral breast recurrence) is 9. Adjuvant endocrine treatment has a small effect on ipsilateral invasive (HR 0.79; 95% CI 0.62–1.01) and DCIS (HR 0.75; 95% CI 0.61–0.92) recurrences and on contralateral invasive (RR 0.57; 95% CI 0.39–0.83) and noninvasive cancer (RR 0.50; 95% CI 0.28–0.87) (endocrine therapy, LoE1a). The number needed to treat to prevent any breast event is 15 [53]. Additionally to established prognostic factors (size, differentiation, margin, histological type) the Oncotype DX DCIS Score [54] and DCISionRT [55] might be useful as prognostic factors for an ipsilateral recurrence after first diagnosis of a DCIS (LoE 2b). The Oncotype DCIS Score is a multigene assay that has been independently validated in a prospective clinical trial and a population-based cohort. The score helps identify a subset of women >50 years old with unifocal disease that carries <10% risk of any local recurrence after breast-conserving surgery alone. DCISionRT provides information regarding the recommendations to add or omit RT.

Oncological Aspects of Breast Cancer Surgery

Surgery is a mandatory part of the multidisciplinary therapeutic approach in EBC. A delay from diagnosis to surgical treatment should be avoided (AGO+). Survival rates after BCS followed by radiation therapy are at least equivalent to those after mastectomy (LoE1a/A). However, surgical treatment decisions should be made within a multidisciplinary conference after a careful pretherapeutic assessment of breast as well as axillary lymph nodes. In non-palpable BC, wire-marking is the standard of care. However (para-)magnetic marker like MagSeedTM can be placed inside tumor during diagnostic procedure. MagSeedTM has shown efficacy as well as non-inferiority in comparison with wire-localization in a prospective clinical trial (LOE 1b/A/AGO+) [56]. Ideally, a lesion should be visualized by ultrasound by the same examiner pre- and intraoperatively. Surgical clip marking of the tumor bed should be performed if boost or partial irradiation is indicated (LoE 2b/B/AGO+) [57]. In patients with pT1/2 cN0 and ≤2 positive SLNs, with breast-conserving surgery, adequate irradiation and systemic treatment, no further ALND should be performed. As it was not clearly defined in the ACOSOG Z0011 protocol, gross extra nodal disease is no exception. 99mTechnetium (Tc) colloid is still the most frequently used technique for SLNE marking. However, as radiotracer production is limited, indocyanine green and super paramagnetic iron oxide are adequate alternatives with at least similar detection rates when compared to 99mTc (LoE 2a/B/AGO+). In patients with clinical as well as sonographical carefully evaluated node-negative disease in tumors less than 2 cm SLNE can be omitted according to SOUND trial [58] (LOE 1b/A/AGO+). However, omitting SLNE should be discussed individually in a multidisciplinary conference. Suspicious lymph nodes should be evaluated prior NACT by core needle biopsy and marker placement. For patients who presented initially with (CNB proven) positive axillary LN (pN+) and converted to ycN0 after NACT, the accuracy of SLNE (LoE 2b/B/AGO +/−) is lower than in the adjuvant setting. Since unselected axillary sampling is not indicated and ALND (LoE 2b/B/AGO+) may be harmful, TAD (LoE 2b/B/AGO+) offers an alternative in these patients. However, in case of extensive axillary tumor load (≥4 suspicious nodes) at presentation, TAD (SLNE plus target lymph node(s) extirpation, TLNE) should be used with caution (LoE 5/D/AGO +/−). In case of residual tumor burden (ypN1mi; ypN+) after TAD, ALND is recommended (LoE 2b/B/AGO+), in case of residual isolated tumor cells only (ypN0[i+]) therapeutic consequence is still unclear and has to be specified in accordance with the results of ongoing studies (LoE 2b/B/AGO +/−; e.g., AXSANA trial) [59].

Oncoplastic and Reconstructive Surgery

Oncoplastic surgery is one of the most essential components in the treatment strategy in breast cancer patients [60]. It is defined as the use of simultaneous reconstructive techniques during breast cancer surgery offering an optimal outcome optimizing quality of life without any compromises toward oncological safety. The use of oncoplastic techniques is based on the surgeon's training and knowledge and should be the basis of planning any breast surgery. Oncoplastic surgery focuses on optimized scar positioning, adequate soft tissue shaping, the choice of a suitable reconstruction procedure, and symmetrization of the contralateral breast.

Breast-conserving surgery can be offered in selected cases of multicentric tumors without increasing recurrence rates (AGO 2b/B/+) [61]. The indication for radiotherapy has the greatest influence on the choice of reconstructive procedure. For implant-based reconstruction, pre- and subpectoral implant placement with or without additional devices (either synthetic mesh or autologous like acellular dermal matrices) can be performed. Current studies such as PREPEC and i-PREPARE investigate whether prepectoral implant placement is superior to subpectoral reconstruction [62]. Perioperative systemic antibiotic prophylaxis for implant-based and autologous reconstruction is recommended (heterologous reconstruction: LoE 1a/A/AGO+, autologous reconstruction: LoE 2b/B/AGO+), but only limited evidence is available on extended antibiotic prophylaxis >24 h (LoE 2a/B/AGO+/−). Topical antibiotics/antiseptics should be used as surgical site infection can be decreased significantly when compared to no topical antibiotics (LoE 2a/B/AGO+); moreover, it reduces the rate of capsular contraction [63]. Regarding prevention of capsular contraction, there is good evidence for textured implants (LoE 1a/A/AGO+) and the use of acellular dermal matrices (LoE2a/B/AGO+) [64] and synthetic meshes (LoE 3a/C/AGO+) when compared to nothing. In cases of presence of capsular contraction, capsulectomy and capsulotomy have old but consistent data (LoE 3b/C/AGO+). If using textured implants or performing capsulectomy/capsulotomy, one has to be aware of breast implant-associated anaplastic large-cell lymphoma BIA-ALCL. Last is a non-Hodgkin lymphoma of T-cell origin. Despite the low incidence of this new disease, the increasing use of breast implants for cosmetic or post-mastectomy reconstruction purposes places BIA-ALCL as an emerging and compelling medical challenge. The pathogenesis is not yet fully understood. Breast implants with textured surfaces seem to be associated with nearly all cases of BIA-ALCL. Late onset, persistent seroma around breast implant represents the most common clinical presentation. Most of the BIA-ALCL patients present with localized disease, which confers an excellent prognosis. Surgical total excision of the capsule is the recommended treatment. For patients with advanced and disseminated diseases, the treatment did not differ from other types of T-cell lymphoma [65]. A new, extremely rare and still virtually unknown carcinoma described in the context of breast implants is the Breast Implant-Associated Squamous Cell Carcinoma. It occurs in patients with long-standing breast implants (>11 years) and presents as breast enlargement/swelling, pain, and skin changes. It is more often associated with poorer prognosis than BIA-ALCL [66]. Therapy of persistent seroma after implant-based reconstruction is lacking robust data. In case of seromas, evacuation and reinsertion of drainage can be performed and revision surgery with capsulectomy or implant removal is recommended as ultima ratio (LoE 5/D/AGO+). There is no consensus for the duration of drains, but the consistent data are in favor of drain removal at <30 mL/24 h (LoE 2b/B/AGO+) [67]. All of the described complications occur significantly more frequently after irradiation. This applies not only to reconstruction with implants but also with autologous tissue [68, 69]. New recommendations on two frequently used adjuncts have been included this year. Tranexamic acid, applied either systemically or topically, has been shown to prevent hematoma and seroma in some studies, but the evidence is not conclusive (LoE 2b/B/AGO +/−) [70, 71]. Topical application of nitroglycerin ointment in the setting of mastectomy with or without reconstruction significantly reduced skin and nipple necrosis rates in meta-analyses [72–74]. Siliconomas can develop in breast parenchyma or regional lymph nodes, rarely in distant organs such as pleura, ribs, muscles, or others after implant placement for reconstruction or augmentation. They may occur with or without implant rupture ("silicone bleeding"). Asymptomatic siliconomas do not require removal (LoE 2b/B/AGO+). In case of implant rupture, complete removal of implant and silicone gel (in capsule, if possible) is recommended (LoE 2b/B/AGO+).

Adjuvant Endocrine-Based Therapy in Pre- and Postmenopausal Patients

In case of ER >10% it is defined as endocrine sensitive and in case of 1–10% (ER low), the tumor is questionably endocrine sensitive. Because ER low tumors can have a similar clinical behavior compared to TNBC, they should be critically discussed in the interdisciplinary tumor conference. In addition, their clinical relevance should be emphasized in the histopathological report. The adjuvant endocrine therapy is divided into initial therapy (years 1–5), extended adjuvant therapy (EAT, years 6–10+), and adjuvant endocrine-based treatment (years 1–2). Standard treatment duration is 5 years. A switch to another better tolerated endocrine treatment (TAM or AI) or TAM low dose is better than stopping endocrine therapy completely (AGO++) [75].

For premenopausal women with low risk of recurrence, therapy with TAM for 5 years is recommended (AGO++). If there is an increased risk of recurrence, therapy with GnRHa plus TAM or AI should be used (LoE1a/A/AGO++). Increased risk of recurrence is not yet clearly defined. By this, decision-making should be performed on an individual basis within the interdisciplinary tumor conference. In case of postmenopausal patients, the initial adjuvant endocrine therapy should be performed with an AI (AGO++) or with a sequential therapy of TAM (2–3 years) followed by AI or with an AI

(2–3 years) followed by tamoxifen to complete 5 years (AGO++).

In patients with an increased risk of recurrence corresponding to criteria of the MonarchE trial, abemaciclib should be given for 2 years (LoE1b/B/+) [76]. The latest update presented at ESMO showed a benefit for invasive disease-free survival (iDFS) after a follow-up of 54 months of 7.6% for abemaciclib plus endocrine therapy versus endocrine therapy alone (HR 0.680 [95% CI 0.599–0.772]; $p < 0.001$). As part of the Natalee study, the use of ribociclib for 3 years was examined [77]. Compared to the MonarchE study, patients with N0 and additional risk factors were also included. The final analysis of the iDFS with a median follow-up of 33.3 months presented a 3-year rate of 90.7% versus 87.6% (HR 0.749 [95% CI 0.628–0.892]; $p = 0.0006$). However, ribociclib as an adjuvant endocrine-based therapy could not yet be included in the AGO recommendations because the corresponding approval is currently lacking.

Olaparib is recommended for patients with germline BRCA1/2 mutations and high risk of recurrence according to the OlympiA study (LoE 1b/B/++). With a median follow-up of 3.5 years, the second interims analysis of OS demonstrated significant improvement in the olaparib group relative to the placebo group (HR 0.68; 98.5% CI 0.47–0.97; $p = 0.009$) [78]. Higher risk of recurrence was defined by CPS-EG score ≥3.

EAT can be recommended for patients with an increased risk of recurrence, e.g., positive lymph node status and/or T2/T3 tumors. In premenopausal women, TAM can be extended for up to 10 years (LoE 1a /A/AGO++). EAT with 5 years of TAM should also be offered to those patients with ovarian suppression and TAM or AI for their initial treatment (LoE 5/D/AGO+). If patients are confirmed as being postmenopausal within the first 5 years, endocrine therapy can be continued after 5 years of TAM with 2.5–5 years of letrozole (LoE 1b/B/AGO+). For postmenopausal women with a high risk of recurrence, extended therapy with 5 years of TAM (after 5 years of TAM) is possible (LoE 1a /A/AGO+) but switching to an AI for 2–5 years should be preferred (LoE 1a/A/AGO++). If patients with a higher risk of recurrence received an AI (upfront or switch), patients with a higher risk should be offered 2–5 additional years of AI (LoE 1a/A/AGO+). The duration of the endocrine therapy in postmenopausal women should not exceed 7–8 years in total because no further benefits were shown [79].

Adjuvant Cytotoxic and Targeted Therapy

Assessment of life expectancy, comorbidities and shared decision-making about possible benefits of (neo)adjuvant therapy are fundamental principles of adjuvant therapy. For the first time, we strongly recommend to split high-risk definition of HR+/HER2-early BC into two groups: those with indication for intensified endocrine therapy (e.g., use of ovarian suppression, longer endocrine treatment and/or use of abemaciclib) and those with an additional indication for (neo)adjuvant chemotherapy. This recommendation is based on increased evidence for lack of chemotherapy benefit in many patients with HR+/HER2-EBC and 0–3 positive lymph nodes and otherwise favorable genomic and biologically risk in particular in >50 years old or in younger node-negative patients irrespective of clinical risk. Regardless of the subtype, dose-dense anthracycline/taxane-based chemotherapy is still the preferred application for adjuvant chemotherapy. A metaanalysis, which is based on individual patient data [80] showed that dose-dense regimens result in a significantly improved 10-year recurrence-free survival and overall survival compared to conventional schedules, irrespective of the subtype. In HER2-positive breast cancer, six cycles of an anthracycline-free regimen containing taxanes/carboplatin is an option (LoE 1b/B/AGO++). In patients with HER2-negative breast cancer docetaxel/cyclophosphamide regimens appear to be an efficacious treatment. In TNBC, the data of adding carboplatin in the adjuvant setting are limited (LoE 1b/B/AGO+) [81], here 18 weeks of paclitaxel/carboplatin have been shown superior DFS compared to three cycles of FEC followed by three cycles of docetaxel. While in the neoadjuvant setting, the addition of carboplatin to anthracyline-/taxane-based treatment has been adopted as a standard treatment, in particular in stage II-III disease which is now supported by a Cochrane metaanalysis [82]. Recently for HER2-negative patients with a high recurrence risk and a germline *BRCA*1/2 mutation olaparib demonstrates as (postneo) adjuvant therapy (LoE 1b/B/AGO+) an improved iDFS and OS [83]. In patients with HER2-positive EBC, neoadjuvant treatment with anti-HER2 therapy is preferred (see chapter NACT). Adjuvant trastuzumab is recommended for node-negative disease with tumors diameter >5 mm–10 mm, if chemotherapy is recommended (LoE 2b/B/AGO+) and highly recommended >10 mm (LoE 1a/A/AGO++). For tumors, <2 cm and node negative 12 × Paclitaxel weekly + trastuzumab for 12 months might be a good anthracycline-free option (LoE 2b/B/AGO+). In tumors, >2 cm and/or node-positive trastuzumab and pertuzumab are recommended as anthracycline-free combination with docetaxel and carboplatin (LoE 1b/A/AGO+) or in the classical sequence AC/EC (q3wks or q2wks + G-CSF) followed by a taxane (LoE 1a/A/AGO++). The data from the APHINITY-trial support adjuvant pertuzumab in addition to trastuzumab and chemotherapy in patients with node-positive disease in HER2-positive EBC (LoE 1b/B/AGO++). At a median follow-up of 8.4 years, 8-year invasive DFS in node-positive patients was 86.1% for trastuzumab and pertuzumab versus 81.2% for

trastuzumab alone (OS improvement by 2%). In the node-negative cohort, no additional clinical benefit was evident for the dual blockade (LoE 1b/B/AGO+/−). Extended adjuvant treatment with neratinib in combination with standard endocrine therapy for 12 months showed a significant improvement in iDFS and OS of high risk (mostly stage II–III) HER2 and HR-positive patients who have completed 1 year of trastuzumab based therapy (LoE 1b/B/AGO+). Hence, no prospective data are available after pertuzumab and/or T-DM1 use, indication for this treatment remains unclear in this situation and may be decided on an individual basis. For patients with HR-positive EBC, ET according to the menopausal status is the standard of care. The addition of abemaciclib for 2 years to standard ET resulted in an improved 3-years IDFS and dDFS (LoE 1b/B/AGO+) [84]. Abemaciclib is indicated in patients with ≥4 positive axillary lymph nodes or 1–3 positive lymph nodes and either G3 or tumor ≥5 cm. In high-risk patients with g*BRCA*1/2mt presenting with non-pCR (TNBC) after NACT or CPS-EG score ≥3 (HR positive), or pT2 or node-positive /TNBC) or >4 positive lymph nodes (HR positive) after primary surgery olaparib is recommended for 1 year in combination with ET (LoE 1b/B/AGO++) [83]. Capecitabine is strongly recommended in patients with TNBC and non-pCR in patients treated with anthracyclines and taxanes in the neoadjuvant setting (LoE 2b/B/AGO++) as investigated in patients with locally advanced tumors at presentation in the CREATE-X study and might be discussed in patients with non-pCR after neoadjuvant carboplatinum and/or pembrolizumab at physician's decision (AGO +/−) but without any supporting data. Pembrolizumab use in stage II–III TNBC patients treated with pembrolizumab in the neoadjuvant setting is recommended for 1 year (in particular in cases with non-pCR [LoE 2b/B/AGO++] [in pCR-cases AGO +]) [36]. Patients with HER2+ disease who did not achieve a pCR should receive 14 cycles of T-DM1 (LoE 1b/B/AGO++) [85].

Neoadjuvant Chemotherapy

If chemotherapy is indicated in patients with EBC, NACT should be preferred as the effect of this therapy can be monitored as an in vivo sensitivity procedure. Beside this evidence is suggesting an improvement of prognosis by individualization of neoadjuvant and post-neoadjuvant therapy as a unique feature of the therapy sequence. The most consistent data exist for TNBC or HER2-positive breast cancer. In patients with HER2+ tumors, anthracycline-/taxane-based (AGO+) or anthracycline-free taxane-/carboplatin-based regimen (both AGO++) and trastuzumab (adding pertuzumab in nodal positive disease and/or tumors >2 cm at presentation [AGO++]) are recommended. For HRpos/HER2neg tumors, dose-dense chemotherapy regimens are recommended (AGO++). In TNBC, dose-dense chemotherapy with an anthracycline/taxane-sequence is also the current treatment standard if the tumor size >1 cm at presentation (AGO++). However, in case of TNBC with positive lymph nodes or tumors larger than 2 cm, the immune checkpoint inhibitor pembrolizumab in combination with an anthracycline and platinum-based chemotherapy is the recommendation independent of PD-L1 status [86] (AGO+). After neoadjuvant treatment and subsequent surgery, pembrolizumab should be completed after surgery for additional 9 cycles. Recommendation levels with pCR are LoE 1b/B/AGO+ and without pCR LoE 1b/B/AGO++. An additional option for patients with TNBC and non-pCR is capecitabine (q3w up to 8 courses) after A-T-containing chemotherapy (AGO++). There are no existing data regarding the combination of Pembrolizumab and capecitabine in the postneoadjuvant setting.

For patients with a germline BRCA1/2 mutation, the postneoadjuvant treatment with olaparib is recommend in TNBC with non-pCR as well as in HRpos/HER2neg cancer with non-pCR and a CPS-WG Score ≥3 (AGO++) due to an overall survival benefit [83]. For patients with non-pCR after targeted therapy including dual inhibition for Her2-positive disease, T-DM1 is highly recommended (AGO++) due to a significant overall survival benefit. In case of non-PCR, an additional extended anti-Her2 therapy after 1 year can be offered with neratinib after Trastuzumab for HR-positive and high-risk (e.g., stage II-III) disease with Loe 2b/B/AGO+.

Adjuvant Radiotherapy

Adjuvant radiotherapy of the whole breast after breast-conserving surgery using moderate hypofractionation remains standard of care (LoE 1a/A/AGO++). Omission of radiotherapy is an option in elderly women with low-risk breast cancer and a limited life expectancy (LoE 1a/A/AGO+). Boost irradiation is recommended in premenopausal patients (LoE 1b/B/AGO++) and in postmenopausal patients with risk factors (LoE 2b/B/AGO+) to reduce the risk of local recurrence. For patients ≥50 years with low-risk characteristics (pT1 pN0 R0 G1-2, HR+, non-lobular histology, no EIC), partial-breast irradiation is a valid option. Indications for post-mastectomy radiotherapy (PMRT) were not changed. For irradiation of the thoracic wall, moderate hypofractionation is recommended (LoE 1a/A/AGO++), also in case of breast reconstruction (LoE 1b/B/AGO+) [87]. After ALND, specific irradiation of level I/II is discouraged except for patients with macroscopic residual tumor (LoE 5/D/AGO++) and patients with extensive perinodal soft tissue involvement (LoE 2b/B/

AGO+), based on a recent analysis [88]. For patients who had primary surgery with SLNE, radiotherapy including level I/II in the clinical target volume is recommended for patients with macrometastases who did not receive ALND (LoE 2b/B/AGO+ within ACOSOG Z0011-criteria and LoE 1b/B/AGO++ outside of the criteria). After NACT and SNLE (with 2 or more SN) alone, radiotherapy should be recommended in patients with residual macro- or micrometastases and no axillary dissection (LoE 5/D/AGO+) and should be discussed in patients with cN + who convert to ypN0 or ypN0(i+) (LoE 5/D/AGO+/−). Regional nodal irradiation including the supra-/infraclavicular and internal mammary region should be performed in patients with ≥4 involved nodes (LoE 1a/A/AGO++) and patients with 1–3 positive nodes who have a HR-negative and/or central/medial tumor (LoE 1a/A/AGO+) and should be considered in premenopausal patients who are node negative with a central/medial tumor that is G3 and HR-negative (LoE1a/B/AGO+) [89]. After NACT, whole-breast irradiation, as well as locoregional radiotherapy in patients with locally advanced tumors (T4 and/or N2-3), is recommended irrespective of treatment response (LoE 1a/A/AGO++). Based on the results of NSABP B-51, RNI and PMRT should be discussed with consideration of individual risk factors for patients with cT1-3 cN1 and a pCR (LoE 1b/B/AGO+/−) [90]. If there is residual tumor in the breast, PMRT is still recommended (LoE1b/B/AGO+).

Breast Cancer: Special Situations

In young women ≤40 years of age, interruption (max. 2 years after at least 18 months of previous therapy) of endocrine therapy in case of desire to have children is most likely not associated with short-term survival disadvantage (LoE2b/B/AGO+) [91]. Prognosis of *BC* during pregnancy is not associated with worse outcome if adequate treatment is performed (LoE 3a). However, poorer outcome has been observed, if BC occurs during lactation and within the first year after pregnancy [92]. After the first trimester, chemotherapy with anthracyclines (LoE 2b) or taxanes (LoE 2a) might be safe (AGO++) for mother and fetus, experiences from genital cancer treatment suggest that platinum compounds can also be used (LoE4/AGO+/−). Use of shortly acting G-CSF may be discussed, though only small series of dose-dense chemotherapy ($n < 50$) are reported (LoE 4 C/AGO+/−) [93].

Treatment of elderly should not differ from that of younger women unless the patient expects a short life span for frailty. However, it is important to adequately assess and document the fitness of elderly (e.g., timed-up-and-go test, G8 score or similar instruments).

For treatment of HR-positive male BC, TAM remains standard. AI in combination with GnRH-agonists may also be an effective treatment option (LoE4/C/AGO+) [94]. In general, the ET in male BC patients should adhere to those in premenopausal women, also considering combinations with targeted therapies.

Inflammatory BC should be treated by the triplet of neoadjuvant systemic treatment, mastectomy and radiotherapy of the chest wall and the regional lymph nodes, independent from response to NACT (LoE 2c/B/AGO++) [95]. A delayed breast reconstruction should be preferred (LoE 3b/C/AGO+) [96].

Tumor-infiltrated axillary lymph nodes without primary are most frequently resulting from occult breast cancer. Extensive histopathological is mandatory to exclude other origins; however, if histology considers occult breast cancer as the most likely origin, further clinical diagnostics (e.g., PET-CT) should be omitted. The treatment is performed similar to breast-conserving therapy in node-positive disease with NACT, TAD (if cCR) (LoE 3b/C/AGO+/−) [97], and radiation of the regional nodes and the breast even if no primary has been detected (e.g., by MRI of the breasts) (LoE 2cB /AGO++).

Fibroepithelial lesions with rapid growth or size >3 cm should be excised (independently from the any CNB result) (LoE 5 D/AGO ++). According to the statements of the Canadian Phyllodes Tumor Consensus Panel (Bogach, 2023 #112), only in malignant phyllodes tumors broad lesion-free margins are required and re-resection is recommended if pathologically less the 2 mm are free of tumor (LoE 2b B/AGO ++). Adjuvant radiotherapy is indicated depending on size, biology and pathological margin status (LoE 2b B/AGO +).

Outcome in secondary, radiation-associated angiosarcoma of the breast does not seem to be improved by more radical surgery. In case tumor-free margins can be achieved, breast-conserving surgery might be an option [98]. The decision for (neo)adjuvant cytotoxic treatment should be made based on individual risk factors (LoE 3a/C/AGO+/−) since radiation-associated angiosarcoma of the breast does not respond well to chemotherapy. However, recently a small study showed a substantial improvement of disease control and reduction of mortality by applying a trimodality therapy that consisted of preoperative taxane therapy followed by taxane-based radiochemotherapy followed by surgery [99] (LoE 3a C/AGO+).

Metaplastic BC is relative chemoresistant and primary surgery and axillary staging according to standard is recommended (LoE 4/C/AGO++). Therapy highly depends on the subtype, thus reference pathology should be considered. However, also in some metaplastic BC NACT may be an option by applying ICPi-based regimen in TNBC (LoE 4 C/AGO +/−) or HER2 directed therapies in HER2-positive cases (LoE 4 C/AGO+). In any case, short-

term controls of response must be performed in order to avoid potential progression during NACT resulting in inoperability (LoE 4/C/AGO–) [100].

Breast Cancer Follow-Up

Less intensive follow-up for patients with DCIS (clinical examination all 6 months) versus patients with invasive BC (all 3 months) is recommended. Still, the rationale of breast cancer follow-up is the early detection of curable breast cancer events (LoE 1a/B/AGO++). Early detection of symptomatic metastases is desirable (LoE 3b/C/AGO+); however, with regard to the early detection of asymptomatic metastases (LoE 1a/A/AGO–), data are inconsistent and, most importantly, does not suggest a survival benefit. Beyond improvement of survival, additional issues like improvement of quality of life and physical performance and the reduction and early detection of treatment-related side effects are important concerns in this matter (LoE 2b/B/AGO+). We added recommendations on cardiologic work-up (echocardiography, BNP measurement in selected cases) in patients treated by anthracyclines/anti-HER2 agents in the adjuvant situation 6, 12, 24 months and yearly up to 5 years after therapy and after the 5th year every 5 years and if the patient is symptomatic according to international guideline [101]. In addition, re-evaluation of current adjuvant therapies (including re-evaluation of menopausal status and change and/or addition of ovarian suppression in high-risk premenopausal patients with chemotherapy-induced amenorrhea) and the assessment or improvement of treatment adherence is an essential part of follow-up care (LoE 2b/B/AGO++). Thus, it should be pointed out that every patient has the right to obtain a second opinion (LoE 2c/B/AGO++); genetic counseling should be offered if indicated, as should HRT, prophylactic surgery, and breast reconstruction (LoE 2c/C/AGO+).

Lifestyle modifications such as nightly fasting over 13 hours and interventions with regard to comorbidities such as type II diabetes are further important aspects of follow-up. Most importantly, follow-up examinations of asymptomatic patients in routine situations should not include tumor marker measurements and imaging of any kind. For the detection of curable events, physical and self-examination with MG and adjunctive ultrasound as well monitoring of treatment toxicity (e.g., of endocrine therapy) are recommended. Follow-up of male breast cancer patients should follow the same procedures as in female breast cancer patients (LoE 5/D/AGO+). Unfortunately, there are still no data that would support tailoring breast cancer follow-up according to molecular subtype. In case of increased risk such as age <50 years, HR negativity, and decreased diagnostic accessibility C/D in MG and ultrasound, magnetic resonance imaging should be considered [102]. In this context, screening for secondary malignancies according to guidelines is meaningful. Patients and physicians should be aware of increased risk of hematologic malignancies after chemotherapy and lung cancer after radiotherapy to the breast or chest wall. Further, a DXA scan at baseline and a repeated scan according to individual risk in women with premature ovarian failure or in women on AI therapy are recommended [103].

Osteooncology

Bone-health issues in breast cancer patients are related to treatment of bone metastasis, prevention of metastases, and cancer therapy-induced bone loss. Current AGO recommendations are based on ESMO Clinical Practice Guideline for bone health in cancer patients [104].

The favorable skeletal effects of denosumab reverse quickly upon its discontinuation because of an increase of osteoclast number and activity, which leads to a subsequent profound increase of bone turnover above pretreatment values, a phenomenon described as “rebound phenomenon” [105]. Therefore, subsequent antiresorptive treatment with a bisphosphonate is recommended. The AGO recommendation is to give bisphosphonates for 1–2 years after discontinuation of denosumab. Adjuvant bone targeted therapy to improve prognosis with clodronate or aminobisphosphonates (1a/A/+) is widely accepted in postmenopausal patients irrespective of HR- or HER2-status. Noteworthy, the NHS PREDICT tool provides estimates of the benefit of therapy and may help in decision-making processes (https://breast.predict.nhs.uk/). Denosumab (6 × 120 mg/3–4w + 14 × 120 mg/3 m) is not recommended for improvement of prognosis in EBC and stage II/III. For postmenopausal patients, undergoing AI therapy denosumab (60 mg SCq6m) is an option (LoE1b/B/AGO+/–) [106]. As therapeutic agents and for the improvement of survival the AGO panel provides a list of recommended bisphosphonates including adjuvant regimens for clodronate, ibandronate, and zoledronic acid. For treatment of tumor-therapy induced bone loss, bisphosphonates and denosumab are strongly recommended (for both LoE1b/B/AGO++). Further recommendations comprise physical activity, calcium/vitamin D supplementation and to avoid immobilization (all ++). As preventive agent bisphosphonates should be given preference (AGO+) over denosumab (AGO+/–). Preferred medical treatments of osteoporosis are bisphosphonates and denosumab (AGO ++). In addition, parathyroid hormone, strontium ranelate, teriparatide, and romosozumab are further options (AGO+).

Treatment with these agents should be planned in cooperation with an osteo-endocrinologist based on the current DVO guideline for osteoporosis (revised in September 2023).

Complementary Therapy and Survivorship

Physical exercise and training (moderate endurance training three times weekly combined with strength training on machines twice weekly) have positive effects on quality of life, cardiorespiratory fitness, physical performance, sleep, pain, depression, lymphedema, fatigue, etc. (LoE 1a/A/AGO ++) [107]. There is evidence that mind-body interventions such as Mindfulness-Based Stress Reduction (LoE 1a/A/+), Yoga (LoE 1b/A/+), or Tai Chi/Qi Gong (LoE 2a/B/+/−) among others, improve quality of life as well as fatigue, etc., in breast cancer patients. Acupuncture is effective in improving side effects of breast cancer treatment such as pain (cancer- and AI-induced) [108], nausea and vomiting (chemotherapy-induced), and fatigue (LoE 1b/B/AGO+). Acupuncture can assist in alleviating sleep problems, cognitive dysfunction (LoE 2b/C/AGO+/−), and polyneuropathy (LoE 2b/B/AGO +/−). Short-term fasting during 3-week chemotherapy cycles reported lower toxicity, reduced fatigue, and improved quality of life in breast cancer patients (LoE 2b/B/AGO +/−) [109]. Extreme fasting or diets should not be recommended to patients (LoE 2a/B/−−); instead, a fiber-rich diet should be pursued (LoE 2a/B/AGO+). Some small RCT-studies have shown that melatonin might has beneficial effects in reducing fatigue and depression symptoms, improving sleep quality and cognition for patients (LoE2b/B/AGO +/−).

Gynecological Issues in Breast Cancer Patients/ Contraception

A metaanalysis including 4,000 patients confirmed the contraindication for systemic HRT to mitigate menopausal symptoms in patients with hormone-receptor positive disease (LoE 1a/B/AGO−). In hormone-receptor negative disease the risk for breast cancer recurrence under HRT was not elevated and HRT might therefore be used (LoE 1a/B/AGO+/−) [110]. The topical vaginal application of low-dose estriol is also an option for urogenital symptoms (LoE 4/D/AGO+/−).

Fertility counseling on fertility preservation (https://fertiprotekt.com) should be offered to all patients who wish to retain their fertility (AGO++). Application of GnRH analogs >2 weeks prior chemotherapy has shown an improved rate of recovery of ovarian function after 2 years independent of the HR status (LoE 1a/A/AGO+) and might have a moderate effect on preservation of fertility (LoE 2a/B/AGO+/−). New statements have been made regarding the oncological safety of fertility preservation methods and assisted reproductive therapy. In general, evidence is limited due to studies with poor quality(e.g., prospective randomized trials are not feasible). The use of GnRH analogs for protection of ovarian functions has no negative impact on survival based on a large metaanalysis (LoE 1a/A/AGO++) [111]. Cryopreservation of ovarian tissue is also oncological safe. However, there is a risk of relapse caused by the transplantation of ovarian tissue after oncological treatment since the tissue may contain tumor cells from the original malignancy (LoE 4D/AGO+) [112]. In BRCA1 1/2 mutated breast cancer patients, transplanted ovarian tissue should be removed after successful pregnancy due to the high risk of ovarian cancer. Cryopreservation of oocytes (unfertilized /fertilized) after ovarian stimulation is another important option for patients before (LoE 2a/C/AGO+) and after anticancer treatments (LoE 4/C/AGO+). So far, no safety concerns have been raised. The short-term increasing hormone levels by ovarian stimulation did not negatively effect the survival outcome of breast cancer patients [113].

Health Literacy and Communication

Health literacy is influenced both by individual abilities and skills ("personal health literacy") and by the demands and complexity of the living environment and systems ("organizational health literacy"). Digital health literacy is the ability to search for, find, understand, and evaluate health-related information in relation to digital applications and digital information services and to apply the acquired knowledge to solve a health problem [114].

Healthy people as well as patients should be instructed and involved as "experts in their own affairs" during the process of preventing and treating cancer. The main focus is on enabling a self-determined decision on the basis of a sufficient healthy competence (LoE3a/AGO+) and improving shared decision-making, which depends on successful doctor-patient communication. In the era of increasing digitalization, the need for education and action with regard to digital health literacy of patients and health professionals is inevitable. Good communication skills are a medical core competence and the basis for a trusting doctor-patient relationship. Qualified training measures can help to promote communicative skills (LoE 2a,b/AGO+). Successful communication and the development of a trustful doctor-patient relationship is an important cornerstone for patient participation in the shared decision-making process. The use of decision support in the physician-patient communication (AGO+) will improve knowledge, information and risk perception about treatment options, reduce the decision

conflict, increase the feeling about clarity of personal values, encourage an active role in decision-making and improve the match between the chosen option and the patients' values. Moreover, decision coaching based on evidence-based patient information can improve the decision-making process of patients. Decision coaching is able to improve the knowledge of patients and their active role in the process of decision-making (LoE/2a,b/B/AGO +). Active involvement of caregivers and trusted persons should be integrated in decision processes (LoE 4/C/AGO+). The use of eHealth (DiGA) can help improve quality of life during and after breast cancer treatment, the use of PROs can help improve the assessment of therapy-associated side effects and quality of life (LoE 2b/B/AGO +/–) [115].

Conclusion

The recommendations of the AGO Breast Committee presented here reflect the rapid development of diagnostic and therapeutic options for early breast carcinoma in recent months and years.

Conflict of Interest Statement

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