Arbeitsgemeinschaft Gynäkologische Onkologie recommendations for the diagnosis and treatment of patients with early breast cancer: update 2023

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Arbeitsgemeinschaft Gynäkologische Onkologie Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2023

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Abstract
Background: Each year the interdisciplinary Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), German Gynecological Oncology Group Breast Committee on Diagnosis and Treatment of Breast Cancer provides updated state-of-the-art recommendations for early and metastatic breast cancer. ***Summary:*** The updated evidence-based treatment recommendation for early and metastatic breast cancer has been released in March 2023. ***Key Messages:*** This paper concisely captures the updated recommendations for early breast cancer chapter by chapter.

Introduction

Breast cancer (BC) 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 BC requires a multidisciplinary strategy. Each year the interdisciplinary AGO Breast Committee (Arbeitsgemeinschaft Gynäkologische Onkologie, German Gynecological Oncology Group) provides updated state-of-the-art recommendations on the prevention, diagnosis, and treatment of BC. 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 and the AGO Grades of recommendation.

The updated recommendations for EBC and MBC of the AGO Breast Committee have been released in March 2023. This paper captures the updated recommendation of EBC. The live stream of the AGO mamma State of the Art including the updated slides with the annotated speeches (German and English) and the Patient Forum is available in the on-demand library (https://www.ago2023.de).

Options for Primary Prevention and Lifestyle Factors

Individual risk factors can be classified into non-modifiable such as age, gender, genetic characteristics, family history, and late menopause and modifiable lifestyle factors. There is growing evidence that changes in modifiable risk factors could substantially decrease individual BC risk [2]. Risk factors that significantly contribute to the development of BC are late pregnancy, nulliparity, hormone replacement therapy (HRT) including estrogen/progesterone combinations, overweight/obesity in the postmenopausal period [2]. Alcohol consumption (LoE2a/B) and cigarette smoking (LoE2a/B) are well-known risk factors. Pregnancy-related factors like number of full-term pregnancies (LoE2b/B), first delivery before the age of 30 years (LoE2b/B), duration of breastfeeding (LoE3a/B) reduces the risk of BC [3]. PCO syndrome may possibly have an unfavorable impact

(LoE3b/C) [4], whereas assisted reproduction (LoE2b/B), and abortion (LoE2b/B) do not influence the risk for BC. Though current use of oral contraceptives slightly increases the risk of BC, it does not increase mortality (LoE1a), and it reduces the risk of ovarian and endometrial cancer [5]. Physical activity (metabolic equivalents to 3–5 h moderate pace walking per week) has been demonstrated to be efficient in reducing BC risk (LoE2a/B/AGO++) particularly for BRCA1/2 mutation carriers and for women with family risks [6]. Adherence to normal body weight (BMI 18.5–25 kg/m^2), particularly for postmenopausal women (LoE 2a/B/++), as well as the prevention/screening and treatment of diabetes mellitus type II (LoE2b/B/AGO++) has an effect on the reduction of BC incidence and mortality [2]. A balanced Mediterranean diet including extra virgin olive oil (LoE2b/B/AGO+) [7, 8], nuts (>10 g/die) (LoE 2b/B/AGO+), reduced consumption of fat (LoE2a/B/AGO+), and red meat (LoE2b/C/AGO+) may decrease the incidence of BC [2]. With regard to medical primary prevention, Acetylsalicylsäure, COX2-inhibitors (LoE2a/B/AGO+/–), bisphosphonates, vitamin D (LoE2b/B/AGO+/–), might reduce BC risk, whereas statins rated (LoE2b/B/AGO–). In women with BC adjuvant endocrine therapy reduces the risk for ipsi-and contralateral second BCs, too (tamoxifen, aromatase inhibitors [AIs] (LoE1a/A/AGO+), GnRH-agonist + tamoxifen (LoE 1b/B/AGO+).

BC Risk, Genetics, and Prevention

With regard to genetic testing, the AGO Breast Committee recommends comprehensive counseling based on family and individual history (LoE2b/B/AGO++) [9], comprising intensive assessment for syndrome-associated BC (non-BRCA; LoE 2b/B/++). Genetic testing for pathogenic variations includes BRCA1/BRCA2 (LoE1b/A/AGO++), PALB2 (LoE3a/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. Mutations in BRCA1/2 and PALB2 are associated with an increased lifetime risk for BC of approximately 40%, for ATM, BARD1, CHEK2, RAD51C, and RAD51D, 20–30%, respectively [10]. Genetic counseling for pathogenic mutations of PALB2, as genes with moderate or lower penetrance [11], has to consider risk as continuous rather than categorical variable, influenced by family history, competing risks, and polygenic traits. Genetic testing of BRCA1/2 germline mutations (gBRCA1/2mut) is recommended to patients under 60 years of age with triple-negative BC, or in case of therapeutical need (e.g., PARP inhibitors) [12, 13]. With estimated high risk for BC, intensified surveillance as well as risk-reducing surgery can be offered. However, without proven genetic risk, risk-reducing surgery should not be offered (LoE2a/B/–).

BC Diagnostics

In asymptomatic women, screening mammography (MG) is highly recommended for women 50–69 years of age (LoE 1a/A/AGO++), with adding the age-group 70–75 as planned, the recommendation expands also to these women (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/B/AGO+) and 70–74 years individual shared decision-making is recommended and clear indication is necessary. 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+/–) [14]. Breast density is a known risk factor for BC development and decreased MG sensitivity. Nevertheless, neither use of handheld US nor automated whole-breast US can be recommended as a sole modality for screening (LoE 3a/C/AGO–) [14]. Using digital breast tomosynthesis, the recall and biopsy rates were low (LoE 1a/A/AGO+) [15–18]. Synthetic 2D image reconstruction of the 3D dataset can significantly reduce radiation dose and is highly recommended (LoE 1a/A/AGO++) [16, 19]. Nevertheless, it is very important to use the complete dataset for diagnosis and provide it for the subsequent treatment [13]. In a randomized controlled trial, MRI 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+) [20, 21]. 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 [22, 23]. As part of surgical planning procedure, ultrasound of the breast (LoE2b/B/AGO++) and the axilla is recommended (LoE2a/B/AGO++) [24, 25]. MRI can be helpful for patients with a reduced sensitivity of MG and US, nipple involvement, lobular invasive cancer, suspicion of multilocular 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 [22]. 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 (NACT) including CT (chest/abdomen) and bone scans (LoE 2b/B/AGO+). PET-CT should be reserved for individual cases with high-stage (III) cancer (LoE 2b/B/AGO+/–) [26].

Pathology

Within the last decades, great advances have been made in early diagnosis and less toxic primary therapy. Many of the advances in pathology have been in conjunction with efforts to support clinical initiatives, improve diagnostic reliability and translate basic science discoveries into tests that stratify patient management. Pathologists together with specialized clinicians have led significant advancements in the description and clinical significance of benign and malign breast disease. Despite considerable efforts, the cure for BC awaits better understanding of the pathophysiology of metastasis. We stand now at the border of a new era of technology, in which genomic assays may be put to use in uncovering targets of therapy and defining mechanisms of invasive disease progression.

Besides the routinely indicated pathological evaluation of the tumor (histologic tumor type (LoE3b/C/AGO++) taken by core needle biopsy particular attention is paid to the immunohistochemical determination (estrogen and progesterone receptor [LoE1a/A/AGO++], Her2 [LoE1a/A/AGO++], reporting of Ki-67 positive nuclei as percentage [LoE5/D/AGO++], grading [LoE5/D/AGO++]). Currently, a subset of HER2-negative BCs with HER2 present but low (HER2-low) has been described to be of therapeutic importance in advanced and pretreated BC (LoE1b/A/AGO++) [27, 28]. Therapy decisions should be based on reevaluation of the HER2 status, including metastases.

In the case of clearly triple-negative EBC (TNBC), there are clear therapeutic procedures. But the recommendations become more difficult if ER or PR is only low positive. Therefore, the use of diagnostic terms, in histopathology must be carefully weighted in the light of clinical decision-making. It has become evident that invasive BC of no special type having low hormone-receptor and negative HER2 status shows similar response to NACT and adjuvant chemotherapy as TNBC. Therefore, patients with low HR expression are candidates for therapy strategies targeting TNBC [29] and a 10% cutoff of ER expression has been recommended [30]. Clearly, this should be restricted to BC of no specific type sharing other characteristics of TNBC, such as high Ki-67.

Also, in this edition of the AGO recommendations, we have outlined three rare categories of TNBC with specific tumor biology, clinical behavior, and treatment response. This includes apocrine TNBC, metaplastic TNBC, and TNBC characterized by specific molecular alterations. Apocrine TNBC is characterized by luminal phenotype (no basal markers), high expression of the androgen receptor, and low tumor proliferation. Clinically, patients with apocrine TNBC is older, has smaller tumors, and a better survival, compared to non-apocrine TNBC [31, 32]. These patients may be subject to de-escalation in systemic therapy [33]. TNBC with specific molecular alterations include adenoid-cystic carcinoma [34, 35], secretory carcinoma [36], polymorphous carcinoma [37], or the tall cell carcinoma with reversed polarity [38]. Generally, these rare types of TNBC are characterized by a more favorable outcome, compared to TNBC of no special type. Within this year, the predictive PD-L1 assay CPS (combined positive score) is rated the same as the IC (Immune Score) based on the new valid data of the keynote studies, which are presented in more detail in the chapter of 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 in situ [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 BC. 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 (LoE3a/C/AGO+). In cases of biopsy of classical LIN open excision can be avoided if no discordant imaging, especially no focal lesion is present (LoE2b/C/++) [39]. 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 (LoE2b/C/AGO++). Flat epithelial atypia is upgraded to DCIS or invasive BC in 5% of all cases. Open biopsy is recommended (LoE2b/B/AGO+) if vacuum biopsy could not remove ≥90% of the lesion [40]. 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 [41]. Therefore, in case of an atypia or multiple lesions an open biopsy is mandatory (LoE3a/C/++). A radial scar 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 [42]. Medical prevention (e.g., low-dose tamoxifen (TAM) (LoE2b/B/AGO+/−) or AI (LoE 1b/A/AGO+/−)) for lesions with uncertain biological behavior may be performed only in very individual cases [43].

Prognostic and Predictive Factors

Locoregional tumor burden together with tumor biology 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. 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 can help in the decision-making process (AGO 1b/A/+). In the TailorX trial that investigated the Oncotype DX/ Recurrence Score (RS) test, 10,000 women with node-negative HR+/HER2-BC from 5 mm to 5 cm in size were included. Two-thirds of women (n = 6,907) fell into the intermediate risk group (RS 11–25) and were randomized to adjuvant chemotherapy plus endocrine therapy or endocrine therapy alone. After 12 years of follow-up, omission of chemotherapy appeared to be safe in a vast majority of women. Only in women under 50 years of age or premenopausal women, there was a benefit of chemotherapy of 3.2–3.4%, which corresponds to a 5-year metastatic-free survival of 95–96% (vs. 93% without chemotherapy). The benefit was particularly high in premenopausal women with a RS 21–25 (hazard ratio [HR] 2.19) and lower with a RS 16–20 (HR 1.4) by exploratory analysis (Sparano SABCS 2022). Due to the most pronounced effect in women immediately before menopause, it appears unclear whether the effect was addressed to the cytotoxic effect of chemotherapy or chemotherapy-induced amenorrhea [44]. Similar results were retrieved from the RxPonder trial that utilized OncotypeDx in patients with 1–3 positive lymph nodes and HR+/HER2– BC. Patients with RS 0–25 were randomized to chemoendocrine versus endocrine therapy alone. No effect of chemotherapy was seen in postmenopausal women (or in those who were >50 years old) in line with the TAILORx results (5-year recurrence-free survival 91.9% without vs. 91.6% with chemotherapy). It was all the more surprising that this was not the case in premenopausal patients who benefitted from adjuvant chemotherapy regardless of RS results (5-year distant disease-free survival [DDFS] 96.3% with vs. 93.9% without chemotherapy, HR 0.62, p = 0.02) [45].

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 (AGO1a/B/+). Results from an exploratory analysis in the ADAPT trial suggest an excellent survival in RS 0–25 and low post-endocrine KI-67 values (≤10%) without chemotherapy use even in premenopausal women [44, 46]. Combination of postendocrine Ki-67 with genomic assays as a treatment decision-maker is currently under investigation in the ongoing ADAPTCycle trial, which compares chemotherapy versus endocrine therapy plus ribociclib in patients with HR+/HER2– BC.

Ductal Carcinoma in situ

DCIS is a preinvasive lesion that is considered to be a precursor of invasive BC. Nevertheless, not all DCIS will progress to invasion. In addition to MG, which is the main diagnostic tool, pretherapeutic assessment in DCIS should also include breast ultrasound, especially to rule out an accompanying invasive component and solid parts (LoE4/C/AGO++) Breast MRIs may be helpful for assessment of the extension and planning surgical procedure in DCIS (LoE1a/B/AGO+/–), but can lead to over- and underestimations of the extension of the DCIS as it represents an extremely heterogeneous group of lesions with variable potential for progression to invasive disease [47]. Complete surgical excision remains the standard of care (LoE1a/A/AGO++). Almost all guidelines recommend clear margins of 2 mm for pure DCIS 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, LoE3b/B/AGO+). Radiotherapy is commonly recommended after BCS of DCIS (LoE1a/A/AGO++) and also systemic endocrine treatment. Patients should be informed that adjuvant endocrine treatment AND irradiation have no impact on survival (LoE1a) but may have a small effect on ipsilateral invasive and DCIS recurrences (radiotherapy and endocrine therapy) and on contralateral invasive and noninvasive cancer (endocrine therapy, LoE1a). Additionally to establish prognostic factors like DCIS size, differentiation, margin, histological type the Oncotype DX DCIS Score [48], and DCISionRT [49] are included in our recommendation as prognostic factors for an ipsilateral recurrence after the first diagnosis of a DCIS (LoE2b). 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 BC Surgery

Surgery is a mandatory part of the multidisciplinary therapeutic approach in EBC. Delay of ≥4 weeks from diagnosis to treatment should be avoided (AGO+). Survival rates after BCS followed by radiation therapy are at least equivalent to those after mastectomy (LoE1a/A). In non-

palpable BC, wire marking is still the gold standard, but new wireless markers such as radar reflectors and magnetic seeds had been already introduced in clinical routine (LoE2b/B/AGO+/−) [50]. To date, there is no superior marker as no head-to-head comparisons exist. Wireless intraoperative ultrasound localization is associated with a significantly higher negative margin rate compared to wire-guided localization (LoE1a/A/AGO++) [51]. Ideally, the lesion must be visualized by ultrasound by the same examiner pre- and intraoperatively. For this procedure, adequate equipment and training of the surgeon are mandatory. Surgical clip marking of the tumor bed should be performed if boost or partial irradiation is indicated (LoE2b/B/AGO+) [52]. 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 extranodal 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 (LoE2a/B/AGO+). 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 (LoE2b/B/AGO+/−) is lower than in the adjuvant setting. Since unselected axillary sampling is not indicated and ALND (LoE2b/B/AGO+) may be harmful, TAD (LoE2b/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 (LoE5/D/AGO +/−). Caudle et al. described a significant reduction of FNR from 10.1% with SLNE alone to 4.2% with TLNE alone, and 1.4% in case of combination of SLNE and TLNE (TAD) [53]. This was nicely confirmed by the SENTA trial [54]. Impact of different TAD staging procedures on disease-free survival and quality of life are lacking. In case of residual tumor burden (ypN1mi; ypN+) after TAD, ALND is recommended (LoE2b/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 (LoE2b/B/AGO +/−; e.g., AXSANA trial) [55].

Oncoplastic and Reconstructive Surgery

Oncoplastic surgery is one of the most essential components in the treatment strategy in BC patients [56]. It is defined as the use of simultaneous reconstructive techniques during BC 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 reconstruction of the contralateral breast in order to achieve symmetry. New data presented at SABCS 2022 confirmed also oncologic safety in multicentric tumors that can be removed via quadrant resection and therefore no longer require mastectomy (AGO 2b/B/+) [57]. But unfortunately, valid evidence is lacking for the majority of important questions. For implant-based reconstruction, pre- and subpectoral implant placement with or without additional devices (either synthetic or autologous like acellular dermal matrices) can be performed. Retrospective data of a current meta-analysis favored prepectoral placement [58], but data from the OPBC prospective study should be awaited for a clear recommendation [59]. Perioperative systemic antibiotic prophylaxis for implant-based reconstruction is recommended to be performed no longer than 24 h (LoE 2a/B/AGO+), and topical antibiotics/antiseptics should be used frequently as surgical site infection can be decreased significantly when compared to no topical antibiotics (LoE2a/B/AGO+); moreover, it reduces the rate of capsular contraction [60]. Regarding prevention of capsular contraction, there is good evidence for textured implants (LoE1a/A/AGO+) and the use of acellular dermal matrices (LoE2a/B/AGO+) [61] and synthetic meshes (LoE3a/C/AGO+) when compared to nothing. In cases of presence of capsular contraction, capsulectomy and capsulotomy have old but consistent data (LoE3b/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 (see also chapter special situations with included recommendations). 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 real BIA-ALCL pathogenesis has not been fully uncovered so far. 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 classical clinical presentation. Most of the BIA-ALCL patients presents with localized disease, which confers an excellent prognosis. Surgical excision is the recommended treatment. For patients with advanced and disseminated diseases, the treatment did not differ from other types of T-cell lymphoma [62]. A very new and extremely rare and still virtually unknown carcinoma disease described in the context with breast implants is the capsule-associated squamous cell carcinoma. It occurs in patients with long-standing breast implant

augmentations (>11 years) and occurs with breast enlargement/swelling and pain and skin changes. It is more often associated with poor prognosis than BIA-ALCL [63]. Therapy of persistent seroma after implant-based reconstruction is lacking robust data. Evacuation of seroma and reinsertion of drainage can be performed and revision surgery with capsulectomy or implant removal is recommended as ultima ratio (LoE5/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 (LoE2b/B/AGO+) [64]. All of the described complications occur significantly more frequently after irradiation. This applies not only to reconstruction with implants but also with autologous tissue [65, 66]. Although used much less frequently than other methods, breast reconstruction with an omentum flap was included this year. Very good cosmetic results can also be achieved with this reconstruction method (AGO 4/C/+/–) [67].

Neoadjuvant Chemotherapy

If chemotherapy is indicated in patients with EBC, NACT should be considered, specifically in patients with TNBC or HER2-positive BC. 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 (AGO++) are recommended. In case chemotherapy is indicated in 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 (AGO++). In patients with positive lymph nodes or a tumor larger than 2 cm pembrolizumab in combination with an anthracycline and platinum-based chemotherapy is an option for TNBC patients independent of PD-L1 status [68] (AGO+). After the completion of the neoadjuvant treatment and the subsequent surgery, pembrolizumab should be completed after surgery for further 9 cycles. Recommendation levels with pCR are LoE 1b/B/AGO+ and without pCR LoE1b/B/AGO++. In both subtypes, TNBC and HRpos/HER2neg olaparib is recommended in patients with germline BRCA1/2 mutation and an increased recurrence risk (AGO++) due to an overall survival benefit [69].

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 have strongly recommended 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 favorable genomic risk (as investigated by Oncotype DX or Mammaprint in the prospective TAILORx, RxPONDER, MINDACT, PlanB, and ADAPT trials) 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 gold standard for adjuvant chemotherapy. The basis for this is a meta-analysis, which is based on individual patient data [70] and was able to show that dose-dense regimens have a significant advantage with regard to the 10-year recurrence-free survival and mortality compared to conventional schedules. In HER2-positive BC, six cycles of an anthracycline-free regimen containing taxanes/carboplatin is another option (LoE1b/B/AGO++). In patients with HER2-negative BC, docetaxel/cyclophosphamide regimens appear to be an efficacious treatment. In TNBC, the question of adding carboplatin in the adjuvant setting is scarce of data (LoE1b/B/AGO+) [71], here only 18 weeks of paclitaxel/carboplatin have been shown to have high efficacy compared to three cycles of FEC followed by three cycles of docetaxel, while in the neoadjuvant setting the addition of carboplatin to anthracycline-/taxane-based treatment has been adopted as a standard treatment, in particular in stage II-III disease [72]. Recently for HER2-negative patients with a high recurrence risk and a germline BRCA1/2 mutation, olaparib demonstrates also after surgery (LoE1b/B/AGO+) and therefore in the adjuvant setting an improved iDFS and OS [69]. 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 (LoE2b/B/AGO+) and highly recommended >10 mm (LoE 1a/A/AGO++). For tumors <2 cm and node-negative 12 x paclitaxel weekly + trastuzumab for 12 months might be a good anthracycline-free option (LoE2b/B/AGO+). In tumors >2 cm and/or node-positive trastuzumab and pertuzumab is recommended as anthracycline-free combination with docetaxel and carboplatin (LoE1b/A/AGO+) or in the classical sequence AC/EC (q3wks or q2wks + G-CSF) followed by a taxane (LoE1a/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 (LoE1b/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 (LoE1b/B/AGO+/−). Extended adjuvant treatment (EAT) 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 (LoE1b/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-yrs IDFS and DDFS (LoE1b/B/AGO+) [73]. 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 gBRCA1/2 mt 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 (LoE1b/B/AGO+) [69]. Capecitabine is strongly recommended in patients with TNBC and non-pCR in patients treated with anthracyclines and taxanes in the neoadjuvant setting (LoE2b/B/AGO++) as investigated in patients with locally advanced tumors at presentation in the CREATE-X study and should discuss in patients with non-pCR after neoadjuvant carboplatinum and/or pembrolizumab at physician's decision (AGO+/−), due to lacking of any pro/retrospective data in this setting duration of 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 (LoE2b/B/AGO++ (in pCR-cases AGO+)) [68]. Patients with HER2+ disease who did not achieve a pCR should receive 14 cycles of T-DM1 (LoE1b/B/AGO+) [74]. It remains unclear whether an additional use of neratinib in patients with non-pCR and HR+/HER2+ high-risk cases would further improve outcome (AGO+/−)

Adjuvant Endocrine Therapy

Endocrine therapy is indicated in all patients with hormone receptor positive EBC (LoE1a/A/AGO++). A meta-analysis of the German Breast Group (GBG) of several neoadjuvant trials suggests that tumors with low HR expression (≥1–9%) behave similar to TNBC, biologically. Thus, omitting endocrine therapy may be an option in cases with very low expression of ER and PR (AGO+) [29]. In case of ER−/PR+ (>10%), immunohistochemical reevaluation of HR should be performed. False positivity for PR should be excluded. Treatment duration of 5 years remains standard of care. EAT might be indicated in patients with increased risk of relapse, such as GIII or node-positive disease at presentation. If adjuvant chemotherapy is indicated, endocrine therapy should be given sequentially after chemotherapy (LoE2a/B/AGO+). If targeted therapy with T-DM1 antibody-drug conjugate is indicated in patients with HER2-overexpressing tumors after neoadjuvant therapy, this treatment can be combined with endocrine therapy simultaneously in patients who also have hormone receptor-positive tumors (LoE2b/B/AGO+) [75].

Premenopausal Patients

Premenopausal patients with hormone receptor-positive tumors and a low risk of recurrence should be treated with TAM alone for 5 years (LoE1a/A/AGO++) [76]. The AGO commission also recommends in patients with low risk of recurrence ovarian function suppression (OFS) alone if there are contraindications to TAM (LoE1a//B/AGO+). In the light of TAM shortage, this is an additional aspect to be discussed with the patients. If patients have an increased risk of recurrence (e.g., axillary nodal involvement, high KI-67, previous adjuvant or NACT, etc.), we recommend either the combination of OFS for 2–5 years in combination with TAM for 5 years (LoE1a/A/AGO++) or the combination of OFS with an AI (LoE1a/A/AGO++). The recently presented and published meta-analysis from the EBCTCG-Group [77] and the updated meta-analysis of the TEXT and SOFT trials [78] have shown that a combination of OFS with AI for 5 years is also effective and in some patient groups even superior to the combination of OFS with TAM. From the EBCTCG meta-analysis, the recurrence rate with AI + OFS was 14.7% after 10 years, and 17.5% with TAM+OFS. The BC mortality from the same meta-analysis showed no difference between the two therapy options (7.2% vs. 6.8%). The recurrence by nodal status was 11.7% with TAM+OFS versus 9.3% with AI + OFS in node negative and 20.9% after TAM+OFS versus 17.1% after AI + OFS in patients with 1–3 involved lymph nodes. From the SOFT and TEXT updated meta-analysis, the absolute improvement in overall survival was 3.3% at 12 years with AI + OFS versus TAM+OFS. The absolute reduction in distant recurrence was 2.6% at 12 years with TAM+OFS versus TAM alone. When counseling premenopausal patients, combination of OFS with either TAM or AI and their different side effect profiles should be discussed with the patients.

Adjuvant Endocrine-Based Therapy with CDK 4/6 Inhibitors and PARP Inhibitors

In the last year, several studies published their results with the inclusion of CDK 4/6 inhibitors in the adjuvant and post-neoadjuvant setting and also with PARPi in patients with germline BRCA1 and/or 2 mutations. We recommend a combination of the CDK 4/6 inhibitor abemaciclib for 2 years with standard endocrine therapy (LoE1b//B/AGO+) according to the data from the MonarchE study. This combination newly approved in April 2022 showed a significant improvement in recurrence free and DDFS compared to standard endocrine therapy alone either given as adjuvant therapy or post-neodjuvant therapy for patients with HR-positive, HER2-negative, node-positive, high-risk EBC [73, 79, 80]. Within the OlympiA study, the addition of olaparib to standard endocrine therapy increased DFS and DDFS compared to standard endocrine therapy alone [12, 69]. Note that patients who have hormone-receptor-positive disease and have been treated with neoadjuvant therapy must have a CPS-EG score (BC staging system for assessing prognosis after NACT on the basis of pretreatment clinical stage, estrogen receptor status (E), grade (G), and post-treatment pathologic stage) of 3 or higher according to the risk calculation of Mittendorf et al. [81] or Marmé et al. [82].

Postmenopausal Patients

For the majority of patients, this endocrine adjuvant therapy should consist of a sequence for 2–3 years of TAM and 2–3 years of an AI for a total duration of 5 years. The combination of standard endocrine therapy with abemaciclib for 2 years is recommended in postmenopausal patients who have the inclusion criteria of the MonarchE study [73, 79, 80]. The combination of standard endocrine therapy with the PARP-inhibitor olaparib for 1 year is recommended in patients with BRCA1 and/or 2 germline mutations, who meet the inclusion criteria of the OlympiA study [12, 69].

EAT in Premenopausal Women

TAM can be extended for up to 10 years (LoE1a/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 (LoE5/D/AGO+). If the patient is 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 (LoE1b/B/AGO+).

EAT in Postmenopausal Women

After 5 years of TAM, extended therapy with 5 years of TAM is still an option (LoE1a/A/AGO+) but switching to an AI for 2–5 years should be preferred (LoE1a/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 (LoE1a/A/AGO+). The duration of the endocrine therapy in postmenopausal women should not exceed 7–8 years in total.

Osteooncology

Bone-health issues in BC 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 [83].

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" [84]. 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 amino bisphosphonates (1a/A/+) is widely accepted in postmenopausal patients irrespective of hormone receptor 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/3–4 w + 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 [85] (LoE1b/B/AGO+/–). 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/Vit. 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.

Adjuvant Radiotherapy

Whole-breast radiotherapy using moderate hypofractionation (40–42.5 Gy in 15–16 fractions over 3 weeks) is the standard of care after breast-conserving surgery

(LoE1a/A/AGO++), with ultra-hypofractionation (5 × 5.2 Gy in 1 week) representing an option for selected cases (LoE1b/B/AGO+/−). Boost irradiation is recommended for premenopausal women (LoE1b/B/AGO++) and – depending on the presence of risk factors – for postmenopausal women (LoE2b/B/AGO+). According to the recently presented results of RTOG 1005 and IMPORT-HIGH, moderate hypofractionation with 15 × 2.67 Gy to the whole breast with a simultaneous-integrated boost of 15 × 3.2 Gy to the tumor bed (over 3 weeks) may be used (LoE1b/B/+) [86, 87]. Intraoperative clip placement improves target volume delineation of the tumor bed (LoE2b/B/+). Partial breast irradiation can be used in patients with favorable prognostic factors with two randomized controlled trials now supporting external beam radiotherapy with moderate hypofractionation (LoE1b/A/++). Moderate hypofractionation is also recommended for postmastectomy radiotherapy (PMRT) (LoE1a/A/++), including patients who had breast reconstruction (LoE2b/B/+). Indications for PMRT remain unchanged. Negative hormone receptor status and medial/central tumor location are now the preferred risk factors for indication of internal mammary node irradiation in patients with 1–3 involved lymph nodes (LoE2a/B/+) [88, 89]. There were no changes regarding radiotherapy of the axilla and/or the supra-/infraclavicular lymph nodes. Moderate hypofractionation is safe for regional nodal irradiation (RNI) and can be used as an alternative to conventional fractionation (LoE1b/B/+) [90]. Ultra-hypofractionation should not be used for RNI outside of clinical trials (LoE2b/B/−). In patients with cT1-2 cN0 BC and pathologically negative nodes (ypN0) after NACT, RNI and PMRT should not be used (LoE2b/B/−). Further recommendations for radiotherapy after NACT were not changed. Radiotherapy to the internal mammary nodes should be used with caution in patients with left-sided BC with cardiac comorbidities and/or simultaneous use of HER2-targeted drugs (LoE2b/A/−).

BC: 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 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 (LoE3a). However, there is new evidence that patients diagnosed with BC during lactation and within the first year after pregnancy may have poorer outcome [92]. Standard endocrine treatment of HR-positive male BC remains TAM. AI in combination with GnRH may also be an effective treatment option (LoE4/C/AGO+) [93]. In general, the ET in male BC patients should adhere to those in premenopausal women. Fulvestrant (LoE4/C/AGO+/−) and endocrine combination treatment with CDK 4/6 inhibitors (LoE4/C/AGO+/−) may be offered as palliative systemic treatment.

Inflammatory BC should be treated by neoadjuvant systemic treatment. Mastectomy is the surgical standard approach. A delayed breast reconstruction should be preferred (LoE3b/C/AGO+) [94]. Due to high risk of local recurrence radiotherapy of the chest wall including regional lymph nodes, independent of response to NACT should be performed (LoE2c/B/AGO++) [95]. 95% of patients with occult BC present with positive lymph nodes. The standard surgical approach is the axillary dissection. However, in case of clinical complete remission after NACT, targeted axillary dissection may be considered to reduce surgical morbidity (LoE3b/C/AGO+/−) [96]. Outcome in secondary angiosarcoma does not seem to be improved by radical surgery. In case tumor-free margins can be achieved, breast-conserving surgery might be an option [97]. Secondary angiosarcoma does not respond well to chemotherapy. Therefore, the decision for (neo)adjuvant cytotoxic treatment should be made based on individual risk factors (LoE3a/C/AGO+/−). The incidence of BIA-ALCL is 1: 3,000 in women with textured implants [98]. As written in the chapter of oncoplastic and reconstructive surgery, the standard therapeutic approach is an implant removal combined with a complete capsulectomy including tumorectomy (LoE3a/C/AGO++). The incidence of bilateral BIA-ALCL is 2–4% in patients with bilateral implants, contralateral implant resection should therefore be discussed (LoE4/D/AGO+/−) [99]. In case of extracapsular extension, polychemotherapy should be administered (LoE4/D/AGO+) [100]. Patients with metaplastic breast carcinoma should receive surgery and axillary staging according to standard (LoE4/C/AGO++). Metaplastic BC is relative chemoresistant. To avoid a potential progression during NACT resulting in inoperability, NACT should be avoided (LoE4/C/AGO−) [101].

Locoregional Recurrence

Basically, the local recurrence should always be confirmed histologically. This should include redetermination of estrogen, progesterone, and HER2-neu receptors. The receptor status is an indispensable predictive factor for therapeutic considerations (LoE 3b/B/AGO++). A complete restaging should always be carried out using CT of thorax and abdomen and bone scintigraphy (LoE 2b/B/AGO++). After a previous mastectomy, the aim should be a wide excision of the local recurrence with an R0 resection (LoE 3b/B/AGO++). If prior breast-conserving therapy has been performed, mastectomy is

the gold standard. Another breast-conserving therapy with R0 resection and, if necessary, partial breast irradiation should be discussed with the patient individually (LoE 2b/B/AGO+) [102]. If the axilla is clinically suspicious, lymph node involvement should be confirmed histologically if possible and then an axillary lymphadenectomy should be performed. After R0 resection, systemic therapy should be based on the updated receptor status of the recurrence. This of course includes endocrine therapy for hormone-receptor-positive recurrences (LoE 2b/B/AGO++) as well as chemotherapy (LoE 2b/B/AGO+) [103] or combined chemotherapy with anti-HER2 treatment (LoE 5/D/AGO+). Whole-breast radiotherapy is always indicated after previous breast-conserving surgery without further adjuvant radiotherapy. After mastectomy, the thoracic wall should be irradiated, possibly including the lymphatic system, especially if adjuvant radiotherapy has not been performed before (LoE 2b/B/AGO+). A second irradiation can be carried out after the R1/R2 resection has been carried out (LoE 3b/B/AGO +/−), possibly also as brachytherapy. In the case of a thoracic wall recurrence after a mastectomy, the thoracic wall can be irradiated, possibly including the regional lymphatic drainage pathways. A second irradiation of the thoracic wall can be carried out with R1/R2 resection, if necessary as brachytherapy or with the addition of regional deep hyperthermia with R1/R2 resection. If adjuvant axillary radiation is not available, axillary radiation can be considered after R0 resection has been performed.

Complementary Therapy and Survivorship

Published studies and review articles underline the effects of physical exercise (endurance training 3 times a week) on quality of life, cardiorespiratory fitness, physical performance, sleep, pain, depression, lymphedema, and fatigue (LoE1a/A/AGO++) [104]. Evidence suggests that mind-body interventions, including cognitive, behavioral therapies, relaxation techniques, and meditation, improve quality of life among BC patients, and therefore clinical guidelines include the recommendation (LoE1a/A/AGO+). Acupuncture is effective in improving side effects of BC treatment such as chemotherapy-induced nausea and vomiting (LoE1b/B/AGO+), A induced arthralgia (LoE1a/B/AGO+), cancer pain (LoE1b/B/AGO+), fatigue (LoE1a/B/AGO+) anxiety, and depression (LoE2b/B/AGO+). Some small RCT-studies have shown that melatonin might have beneficial effects in reducing fatigue and depression symptoms, improving sleep quality and cognition for patients (LoE2b/B/AGO+/−). Short-term fasting during adjuvant chemotherapy and radiation treatment reported less toxicity, reduced fatigue and improved quality of life in BC patients (LoE2b//AGO+/−). Extreme fasting should not be recommended to patients looking for complementary treatments (LoE 2a/B/−).

Gynecological Issues in BC Patients/Contraception

Compared to last year's recommendations, minor changes have been made. Leading to a higher level of evidence a meta-analysis including 4,000 patients confirmed the contraindication for systemic HRT to mitigate menopausal symptoms in patients with hormone-receptor-positive disease (LoE1a/B/AGO−). In the case of hormone-receptor negative disease, the risk for BC recurrence under HRT was not elevated and HRT might therefore be used (LoE1a/B/AGO+/−) [105]. The topical vaginal application of low-dose estriol is also an option for urogenital symptoms (LoE4/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 hormone receptor status (LoE1a/A/AGO+) and might have a moderate effect on preservation of fertility (LoE2a/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 meta-analysis (LoE 1a/A/AGO++) [106]. 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+) [107]. In BRCA1, 1/2 mutated BC 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 BC patients [108].

BC 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 BC follow-up is the early detection of curable BC events (LoE1a/B/AGO++). Early detection of symptomatic metastases is desirable (LoE3b/C/AGO+); however, with regard to the early detection of asymptomatic metastases (LoE1a/A/AGO–), data are inconsistent and, most importantly, do 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 (LoE2b/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 [109]. In addition, reevaluation of current adjuvant therapies (including reevaluation 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 (LoE2b/B/AGO++). Thus, it should be pointed out that every patient has the right to obtain a second opinion (LoE2c/B/AGO++); genetic counseling should be offered if indicated, as should HRT, prophylactic surgery, and breast reconstruction (LoE2c/C/AGO+). Lifestyle modifications such as nightly fasting over 13 h 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 BC patients should follow the same procedures as in female BC patients (LoE5/D/AGO+). Unfortunately, there are still no data that would support tailoring BC follow-up according to molecular subtype. In case of increased risk such as age <50 years, hormone-receptor (HR) negativity, and decreased diagnostic accessibility C/D in MG and ultrasound, magnetic resonance imaging should be considered [110]. 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 [111].

Health Literacy and Communication

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 (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 considerable. Therefore, health literacy should be promoted, especially in the areas of media literacy and critical judgement. For this, appropriate formal and nonformal or informal education and teachers with digital and health literacy must support the individual. In addition, framework conditions must be created through low-threshold access to electronic aids, target group-specific offers; participation of the target group in technological development and access to evidence-based, comprehensible offers must be improved. Good digital health literacy can promote digitalization by enabling health professionals to use digital services, use them purposefully in shared decision-making and participate their further development [112]. Good communication skills are a medical core competence and the basis for a trusting doctor-patient relationship. Qualified training measures can help promote communicative skills (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 (AGO+).

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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