

# AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2017

Cornelia Liedtke<sup>a</sup> Marc Thill<sup>b</sup> Christian Jackisch<sup>c</sup> Christoph Thomssen<sup>d</sup> Volkmar Müller<sup>e</sup>  
Wolfgang Janni<sup>f</sup> on behalf of the AGO Breast Committee\*

<sup>a</sup>Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Schleswig-Holstein/Campus Lübeck, Lübeck, Germany;

<sup>b</sup>Klinik für Gynäkologie und Geburtshilfe, Agaplesion Markus Krankenhaus, Frankfurt/M., Germany;

<sup>c</sup>Klinik für Gynäkologie und Geburtshilfe, Sana Klinikum Offenbach, Offenbach, Germany;

<sup>d</sup>Universitätsfrauenklinik, Martin-Luther-Universität Halle-Wittenberg, Halle/Saale, Germany;

<sup>e</sup>Klinik und Poliklinik für Gynäkologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany;

<sup>f</sup>Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Ulm, Ulm, Germany

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## Introduction

For the last 16 years, the Breast Committee of the *Arbeitsgemeinschaft Gynäkologische Onkologie* (German Gynecological Oncology Group, AGO) has been preparing and updating evidence-based recommendations for the diagnosis and treatment of patients with early and metastatic breast cancer. The AGO Breast Committee consists of gynecological oncologists specialized in breast cancer, and interdisciplinary members specialized in pathology, radiological diagnostics, medical oncology, and radiation oncology. This update has been performed according to a documented rule-fixed algorithm, by thoroughly reviewing and scoring chapter by chapter the recent publications for their scientific validity (Oxford level of evidence (LoE), [www.cebm.net](http://www.cebm.net)) [1] and clinical

relevance (AGO grades of recommendation) (suppl. table 1, [www.karger.com/?DOI=477575](http://www.karger.com/?DOI=477575)). We herewith present the 2017 update; the full version of the updated slide set is available online as a PDF file in both English and German [2].

## Options for Primary Prevention: Modifiable Lifestyle Factors

Individual risk factors can be classified into non-modifiable, modifiable, and socially defined factors. Currently, there is good evidence that changes in some modifiable risk factors could substantially decrease individual breast cancer risk.

Relevant lifestyle factors such as obesity, alcohol, physical inactivity, smoking, and low fiber intake are well known, and there is new data from a Dutch retrospective cohort study confirming that 25.7% of cases of postmenopausal breast cancer are associated with lifestyle factors [3].

We would like to stress that obesity (high body mass index, BMI) has a particularly significant influence on the incidence of primary and recurrent breast cancer. There is, however, uncertainty as to whether high BMI is significantly associated with the diagnosis of a triple-negative breast cancer (TNBC) [4].

Changing one's lifestyle has a preventive effect with regard to breast cancer: Maintenance of normal weight, fat-reduced diet, reduced intake of saturated fatty acids, reduction in meat consumption and alcohol intake (particularly for estrogen and progesterone receptor (ER/PR)-positive and/or invasive lobular tumors), smoking cessation, physical exercise, and avoidance of hormonal therapy (especially estrogen/progestin combination regimens) in postmenopausal women are controllable factors that may reduce breast cancer risk.

\*Members of the 'AGO Breast Committee' in alphabetical order: U.-S. Albert, Frankfurt/M.; I. Bauerfeind, Landshut; J. Bischoff, Dessau; J.-U. Blohmer, Berlin; W. Budach, Düsseldorf; P. Dall, Lüneburg; I.J. Diel, Mannheim; P. Fasching, Erlangen; T. Fehm, Düsseldorf; N. Fersis, Bayreuth; M. Friedrich, Krefeld; B. Gerber, Rostock; V. Hanf, Fürth; N. Harbeck, Munich; J. Huober, Ulm; C. Jackisch, Offenbach; W. Janni, Ulm; H. Kreipe, Hannover; T. Kühn, Esslingen; S. Kümmel, Essen; C. Liedtke, Lübeck; S. Loibl, Neu-Isenburg; H.-J. Lück, Hannover; M. Lux, Erlangen; N. Maass, Kiel; G. von Minckwitz, Neu-Isenburg; V. Möbus, Frankfurt/M.; V. Müller, Hamburg; M. Müller-Schimpfle, Frankfurt/M.; C. Mundhenke, Kiel; U. Nitz, Mönchengladbach; Dr. M. Rezaei, Düsseldorf; A. Rody, Lübeck; A. Scharl, Amberg; M. Schmidt, Mainz; R. Schmutzler, Cologne; A. Schneeweiss, Heidelberg; I. Schreier, Hamburg; F. Schütz, Heidelberg; P. Sinn, Heidelberg; C. Solbach, Frankfurt/M.; E. Solomayer, Homburg; E. Stickeler, Aachen; M. Thill, Frankfurt/M.; C. Thomssen, Halle (Saale); M. Untch, Berlin; F. Wenz, Mannheim; I. Witzel, Hamburg

## Breast Cancer Risk and Prevention

Currently, the indication for testing patients for *BRCA1/2* mutations is based upon family and personal history of breast and/or ovarian cancer. Before genetic testing is initiated, counseling and informed consent are mandatory. This should include clinical therapeutic/preventive consequences in the case a mutation is detected. A checklist for evaluating the personal history is available in German [5]. Furthermore, *BRCA1/2* testing should be offered to patients with TNBC being 60 years or younger [6]. Based on a recent cohort study, the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) offers testing to TNBC patients younger than 50 years of age within specialized contracts. Also, 20–30% of genetic test results reveal variants of unknown significance (VUS). This rate can be considerably reduced by additional analyses. Applying the classification of the International Agency for Research on Cancer (IARC), VUS are class 3 aberrations with a probability of being deleterious in 5–95% of cases. Only class 4 and 5 variants with a probability of > 95 and > 99%, respectively, are clinically relevant. As more than 60% of the class 3 variants are extremely rare and population-specific, only large databases such as that of the German Consortium of Hereditary Breast and Ovarian Cancer (GC-HBOC) or ENIGMA allow further classification of most of these variants. More and more variants are described also in publicly accessible databases such as ClinVar that is supported by e.g. ENIGMA and the GC-HBOC [7, 8]. Recent data suggest that besides *BRCA1/2*, which are clear high-risk breast cancer susceptibility genes, possibly *PALB2* might be considered a high-risk gene as well (LoE 3a/B/AGO+/-) [9]. Further new risk genes are currently being identified that need to be validated with respect to clinical validity and utility [10]. Moreover, there are many non-*BRCA*-associated hereditary cancer syndromes with an increased risk for breast cancer (Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer syndrome, Peutz-Jeghers syndrome, Lynch syndrome). The use of commercially available but not validated breast cancer gene panels for risk prediction is not recommended outside of prospective studies. Furthermore, clinical genetic testing for low-risk variants in clinical routine should be avoided (LoE 3b/D/AGO-). For many of these genetically defined subtypes, issues such as histopathological features, sensitivity to different screening modalities, course of disease, or specific treatment response still remain unclear. Like *BRCA1/2*, moderate- and low-risk variants can also be associated with specific breast cancer subtypes. Healthy women who are identified as being at moderate to high risk for disease development should be offered participation in an intensified surveillance program for the detection of early-stage breast cancer (LoE 2a/B/AGO++). Women with *BRCA1/2* mutations should also be offered nondirective counseling for the uptake of primary preventive measures (e.g. risk-reducing bilateral salpingo-oophorectomy at around 40 years of age (LoE 2a/B/AGO++), risk-reducing bilateral mastectomy (LoE 2a/B/AGO+), or medical prevention with tamoxifen (LoE 1a/A/AGO+), raloxifen (LoE 1b/A/AGO+), or an aromatase inhibitor (AI) (LoE 1b/A/AGO+)) in addition to participating in an intensi-

fied surveillance program. However, unilateral or bilateral mastectomy is not indicated in the absence of clearly defined genetic risk factors (LoE 2a/B/AGO+).

New data regarding the clinical benefit of risk-reducing contralateral mastectomy in affected *BRCA1/2* mutation carriers suggested a disease-free and overall survival (DFS/OS) benefit in specific subgroups only, especially in patients aged < 40 years with G1/2 tumors, no TNBC, and no chemotherapy. Therefore, this intervention has to be thoroughly discussed with each individual patient (LoE 2b/B/AGO+/-).

To date, there are no treatment recommendations specific to affected mutation carriers. Breast-conserving therapy (BCT) is safe (LoE 2a/B/AGO+), and systemic therapy can be given according to recommendations for sporadic breast cancer (LoE 3a/B/AGO+).

Based on data from the GeparSixto trial [11], the addition of carboplatin to neoadjuvant chemotherapy (NACT) seems to be beneficial for patients with TNBC regardless of *BRCA1* or *BRCA2* mutation status. Overall, TNBC status in association with a *BRCA1* or *BRCA2* mutation displays an even higher overall chemotherapy sensitivity and better clinical outcome in comparison to patients without a *BRCA1* or *BRCA2* mutation. In the metastatic setting, carboplatin represents an effective treatment option favored over docetaxel in *BRCA*-mutated breast cancer (LoE 2b<sup>a</sup>/B/AGO+). The use of poly(ADP-ribose) polymerase (PARP) inhibitors is currently being validated in prospective randomized studies (LoE 2b/D/AGO+/-), but first data from larger randomized trials points to a benefit in early therapy lines of *BRCA1/2*-mutated HER2-negative metastatic breast cancer in comparison to mono-chemotherapy.

## Breast Cancer Diagnostics

The aim of early detection and screening of breast cancer is to reduce breast cancer-specific mortality and treatment-dependent morbidity. The detection of invasive breast cancer at an early stage (stage I) offers the chance to survive the disease with less treatment-induced impairment and better quality of life [12]. Professionals and women need to be informed about the benefits and harms of cancer screening tests before making medical decisions. This includes clear and understandable information in absolute terms about false-positive rates, false-negative rates (FNR), overdiagnosis, and overtreatment.

All available evidence confirms that mammography screening is capable of significantly reducing breast cancer mortality. Based on a review by Oeffinger et al. [13], the number needed to screen (NNS) to prevent 1 breast cancer death with a mortality reduction of 20% (40%) was estimated for women aged 40–49 years to be 1,770 (753), for women aged 50–59 years 1,087 (462), and for women aged 60–69 years 835 (355). Screening mammography for breast cancer is recommended for women 50–74 years of age [14–19] (LoE 1a/A/+++). For women 40–49 years of age, individual shared decision-making is recommended as these women would have smaller beneficial health effects than women of older age groups, e.g. higher recall rates for additional imaging and biopsy

rates [20, 21] (LoE 1a/B/+). There are no studies on women older than 75 years of age. However, in view of an aging population, screening can be offered to women in good health with a life expectancy of 10 years or longer (LoE 4/C/+).

For breast cancer screening, neither hand-held ultrasound (HHUS) nor automated whole-breast ultrasound (ABUS) alone are recommended (LoE 3b/C/AGO-). The arguments against ultrasound alone as a screening modality are lack of reproducibility, high false-positive rate, low positive predictive value for biopsy, and lack of quality assurance.

The limitations of mammography are well known; hence, new technologies to overcome these constraints are highly welcome. Beside retrospective studies, 4 prospective studies within the European Breast Cancer Screening Program and 3 systematic reviews have been published. Digital breast tomosynthesis (DBT) added to 2D-mammography proved to significantly increase the invasive cancer detection rate and reduced false-positive outcomes. In addition, first results on interval cancer rates showed a decrease. However, the radiation dose with dual acquisition received is increased [22–28].

DBT is recommended if further mammographic diagnostic interventions like digital spot compression view are requested [29, 30] (LoE 3b/B/AGO+).

Mammography has a lower sensitivity and specificity in women with increased breast density, who also have a higher risk of breast cancer. To describe mammographic breast density, the use of BI-RADS breast composition A–D is recommended instead of the former ACR 1–4 category [31, 32]. However, there is no gold standard for density determination as accuracy studies are missing. The recent systematic review by Melnikow et al. [33] (2016) revealed a reclassification rate of 12.6–18.7%. The use of adjunct imaging techniques (DBT, HHUS, ABUS, magnetic resonance imaging (MRI)) in women with dense breast tissue increased the detection rate of cancers (rather than of ductal carcinoma in situ (DCIS)) for all imaging modalities. Harms of supplemental imaging in women with dense breasts included higher recall and biopsy rates for women who do not have breast cancer. With DBT, the recall and biopsy rates were low. Considering recent results of observational studies, HHUS struck the best balance on benefits and harms [34, 35] (LoE 2b/B/AGO++).

To assess breast symptoms or lesions, clinical examination (LoE 3b/B/++), mammography (LoE 1b/A/AGO++), ultrasound (LoE 2b/B/AGO++), and minimal invasive biopsies (LoE 1c/A/AGO++) should be performed. Elastography has some advantages in further characterizing focal breast lesions additionally to B-mode sonography in the differentiation of BI-RADS 3 and BI-RADS 4a lesions in that it decreases the false-positive biopsy rate (LoE 2a/B/AGO+).

Contrast-enhanced MRI plays an important role in acknowledged indications in diagnostic breast imaging as well as in high-risk patients. MRI should not be generally used to assess symptoms or breast lesions. MRI can be used if clinical examination, mammography, and ultrasound do not allow a definitive diagnosis (LoE 2b/B/AGO+/-). Second-look ultrasound is recommended in the case of MRI-only detected lesions (LoE 2b/C/AGO++).

MRI should not be generally used for preoperative staging purposes in the case of BCT. According to a meta-analysis, the re-excision rate was not reduced. Furthermore, the initial and total rate of mastectomy increased if a preoperative breast MRI was performed compared with no preoperative breast MRI. However, in the case of lobular invasive breast cancer, there was a significant reduction in the re-excision rate and no significant impact on the rate of mastectomies with the use of preoperative breast MRI [36, 37]. Preoperative breast MRI did not help to reduce the rate of local recurrences nor improve the local recurrence-free survival or distant metastasis-free survival [38]. It is important to realize that MRI-detected suspicious lesions should prompt MRI-based biopsy or marking for clarification. For some patients, e.g. with a high breast density (density BI-RADS composition C–D), nipple involvement, lobular invasive cancer, suspicion of multilocular disease, and high risk, MRI can be considered (LoE 1b/B/AGO+/-) [39, 40]. MRI-guided vacuum-assisted biopsy is mandatory in the case of MRI-detected additional lesions.

In the case of clinical and/or sonographic suspicious axillary lymph nodes, elastography adds to the diagnostic accuracy. Ultrasound-guided fine needle aspiration or core cut biopsy is recommended to avoid two-step axillary surgery (LoE 2b/B/AGO++). The standard procedure in patients with unsuspected axillary lymph nodes is sentinel lymph node biopsy (SLNB).

## Pathology

When determining ER status, it is recommended to recognize cancers with low receptor expression (> 1–10%) as a biologically distinct group. Breast cancers with borderline hormone receptor (HR) expression (> 1 – < 10%) were initially regarded as HR-negative; however, today they are classified as HR-positive due to a change in the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines. It has to be acknowledged though that the majority of data supporting this was published at a time when immunohistochemistry was not as standardized and sensitive as it is today. In contrast, recent publications [41–44] suggest that tumors with low ER expression share several features such as BRCAness, gene expression profiles, and prognosis with TNBC. Therefore, it is recommended to define these cancers as ‘low positive’ rather than ‘positive’ in histology reporting. Nevertheless, the clinical consequences of this differentiation remain yet unclear.

## Lesions of Uncertain Malignant Potential (B3)

Among the lesions of uncertain malignant potential that have been grouped into the B3 category, the 5 lesions discussed in this chapter (atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), lobular intraepithelial neoplasia (LIN), papilloma, radial scar) are commonly regarded as risk lesions when detected on core biopsy. This is based upon the observation that in a low percentage

of cases these lesions may be associated with or may develop into carcinoma in situ or invasive carcinomas on open biopsy. The accurate pathological identification and classification of lesions with atypical proliferations is important to assess the individual risk of the patient and to decide whether the lesion should be excised. Papillomas and radial scars are included in the B3 category because of their potential for intralesional heterogeneity and atypia. Over the last years, the evidence to guide the management of the treatment of lesions with uncertain malignant potential has grown, and this has led to a more conservative approach in general.

However, the published literature mostly consists of single-institution, non-randomized, retrospective case series, often with a lack of careful pathologic-radiologic correlation and concern about possible selection bias for open biopsy. This may explain the variations in the published upgrade risks to invasive or non-invasive cancer on open biopsy. Taking this into account, the upgrade risk for ADH is estimated at 20–30%, and the upgrade risk for the other lesions in question (FEA, LIN, papilloma, radial scar) at 0–10%.

ADH has a much higher upgrade risk for several reasons, one of them being that the criteria for the diagnosis of ADH were established based on open biopsies some 30 years ago and are now being applied to core biopsies and vacuum-assisted biopsies. Given the fact that the criteria for diagnosing ADH are, in part, quantitative, the upgrade risk for ADH mostly represents an underestimation risk for DCIS. In 1 recent study, 82% of the open biopsies upgraded after the diagnosis of ADH contained DCIS. An international consensus on B3 lesions recommends surgical excision of ADH. After surgical excision of ADH, the breast cancer risk is increased 4-fold [45].

FEA is mostly a clinically occult lesion detected through microcalcifications on screening mammography. Several recent studies that have included radiologic-pathologic correlations show low upgrade risks of below 10%. Therefore, treatment decisions among these patients may be individualized with open biopsy not being necessary in the case of a small lesion ( $\leq 2$  terminal ductal-lobular units on vacuum-assisted biopsy) and complete removal of the imaging abnormality. In an observation-only study of 50 patients with pure FEA, none developed invasive carcinoma or DCIS during a median follow-up of 5 years.

Papillomas most frequently present as solitary or multiple central papillomas and should be distinguished from peripheral papillomas that are often smaller and commonly associated with proliferating breast disease. Patients with multiple central papillomas or atypical papillomas on core needle biopsy should be routinely referred for surgical excision due to a much higher risk of underestimation of cancer. In the case of solitary papillomas, the upgrade risk is much smaller, and, provided that biopsy has been sufficiently representative (100 mm<sup>2</sup>) and no discordance with imaging results is evident, conservative management is usually justified [46].

For LIN, regarding the risk associated with a diagnosis of LIN, it must be considered that in the early literature incidental cases of LIN (which are commonly associated with occult microcalcifications) were often not clearly separated from those with other radio-

logical abnormalities. Consequently, upgrade rates for LIN are commonly reported to exceed 20%. More recent studies with careful radiologic-pathologic correlation have reported much lower upgrade rates for occult lesions with LIN on core biopsy (< 10%) [47]. However, it must be considered that rare variants of LIN with higher risk have been identified, including pleomorphic and florid lobular carcinoma in situ (pLCIS and fLCIS). pLCIS was shown to behave more aggressively compared to classical lobular neoplasia. fLCIS is another form of LIN with high risk, and may not infrequently be associated with microinvasion. In the LIN grading system (LIN 1–3), pLCIS and fLCIS are categorized as the most severe grade (LIN 3) [48].

A radial sclerosing lesion or radial scar may mimic carcinoma mammographically because of its stellate appearance. However, radial scars are generally benign lesions, and recent studies with careful radiologic-pathologic correlation have indicated that open biopsy is not necessary for small lesions and in the case of complete removal of the imaging abnormality.

In conclusion, there is accumulating evidence that open biopsy may not be necessary in many patients with FEA, LIN, papilloma, or radial scar lesions, provided that careful radiologic-pathologic correlation was performed on an individual basis, and the imaging abnormality was completely or at least sufficiently removed. This can often be achieved with a diagnostic-therapeutic vacuum-assisted biopsy [49].

### Ductal Carcinoma in Situ

The diagnosis of DCIS increased dramatically following the introduction of screening mammography, and now comprises approximately > 20% of all newly diagnosed breast cancers [50]. However, epidemiological studies demonstrate that the removal of DCIS lesions has not been accompanied by a reduction in the incidence of invasive breast cancer [51, 52]. DCIS presents as we know a heterogeneous group of neoplastic lesions, and the goal of therapy is to minimize the risk of overdiagnosis, avoid under- or overtreatment, and prevent the development of invasive breast cancer.

DCIS is not usually detectable by clinical examination. Nevertheless, clinical examination remains useful, especially to exclude other clinical abnormalities. DCIS is commonly diagnosed by mammography, but up to 20% of DCIS remain mammographically occult due to the lack of calcifications and/or small tumor dimensions. The use of additional imaging techniques may theoretically be helpful to detect the full extent of a lesion and define surgical treatment. Breast MRI has a high sensitivity in the diagnosis of invasive breast cancer, varying from 90 to 100%. The sensitivity for the diagnosis of DCIS is 77–96% [53]. For the time being, the primary role of MRI in DCIS is limited to the evaluation of lesion extension and thus the planning of breast-conserving surgery (BCS) [54]. The different diagnostic techniques and the evidence of the AGO recommendation are summarized in suppl. fig. 1 ([www.karger.com/?DOI=477575](http://www.karger.com/?DOI=477575)).



Biological characteristics of DCIS often predict recurrence and the type of invasive cancer that may develop in the future. Among patients with DCIS, breast cancer-specific mortality was associated with age at diagnosis, ethnicity, grade, size, and ER status [51]. This information is critically significant in stratifying DCIS patients into prognostically relevant categories. With appropriate risk prediction for subsequent development of invasive cancer that has the potential to claim the life of a woman, there is a better chance for individualized therapy.

BCS aims at the complete removal of the DCIS and represents the more favorable treatment in a majority of patients. Negative margins of at least 2 mm are associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) compared with positive margins defined as ink on DCIS. Negative margins of less than 2 mm alone are not an indication for mastectomy, and factors known to impact rates of IBTR should be considered in determining the need for re-excision [55].

The majority of trials showing that after surgery adjuvant treatments reduce the rate of recurrent DCIS and invasive recurrences have at the same time been unable to show an effect on mortality. Radiotherapy after BCS has been shown to halve both in situ and invasive recurrences in 5 phase III trials, 2 of which have also demonstrated that tamoxifen 20 mg/day reduces the risk of ipsilateral and contralateral events by approximately 30% at both 10 and 15 years (LOE 1a/A/AGO+) [56, 57]. Omitting radiotherapy implies an elevated risk for local recurrence without an effect on OS even in the subset of 'good-risk' patients. There remains a lack of level-1 evidence supporting the omission of adjuvant radiotherapy in selected low-risk cases: < 2.5 cm, low and intermediate nuclear grade, mammographically detected DCIS. Retrospective evaluation of ER status showed that tamoxifen reduced any subsequent breast events by 42% in ER-positive DCIS [58, 59]. In summary, AIs offer another endocrine option for postmenopausal women with ER-positive DCIS, and the choice between an AI and tamoxifen will probably depend more on a previous history of other conditions (e.g. osteoporosis and venous thrombosis) and short-term tolerability (musculoskeletal, vasomotor, and gynecological symptoms) than differences in efficacy.

The optimal management in particular of adjuvant treatment and long-term risks must be discussed with patients. Hence, the potential side effects of radiation therapy and endocrine therapy, albeit small, must be weighed more carefully when making treatment decisions for patients with DCIS.

### Prognostic and Predictive Factors in Early Breast Cancer

Prognostic and predictive factors are an essential part of therapy concepts in early and advanced breast cancer. In 2017, the AGO guidelines for prognostic and predictive factors did not change substantially, since the data presented in 2016 altered mostly evidence levels (LoE) but not the AGO recommendations.

In HR-positive HER2-negative early breast cancer with 0–3 involved lymph nodes, gene expression assays may be used if established clinical pathological factors do not allow therapy decisions regarding the use of chemotherapy in addition to standard endocrine therapy. Patients with an estimated risk of recurrence of more than 10% at 10 years are generally considered candidates for upfront or adjuvant chemotherapy. AGO recommends 4 tests (AGO+) that have been thoroughly validated retrospectively (LoE IB for Endopredict® (Sividon, Cologne, Germany), Prosigna® (NanoString, Seattle, WA, USA)) and prospectively (LoE IA for MammaPrint® (Agendia, Irvine, CA, USA), Oncotype DX® (Genomic Health Redwood City, CA, USA)) for use in clinical routine. In 2016, prospective 5-year outcome data for Oncotype DX® from the WSG PlanB Trial [60] and for MammaPrint® from the MINDACT trial [61] confirmed an excellent outcome in pN0–1 patients who had low-risk test results. Apart from the gene expression profiles, the tumor tissue concentrations of uPA/PAI1 (FEMTELLE®; Sekisui Diagnostics, Lexington, MA, USA) still have the highest evidence levels (LoE 1aA/AGO+) with regard to the identification of those patients with node-negative breast cancer who can avoid adjuvant chemotherapy for having a very low risk of recurrence. Moreover, pooled data suggests that high levels of these markers may predict benefit from chemotherapy [62, 63]. In HER2-positive early breast cancer, a recent meta-analysis (n = 967) demonstrated that pathologic complete response (pCR) after neoadjuvant therapy (chemotherapy + anti-HER2 therapy) is significantly lower in *PIK3CA*-mutant versus -wildtype tumors (16.2 vs. 29.6%; p < 0.001) (LoE IB). This difference was mostly due to a substantial difference in HR-positive tumors with pCR rates of 7.6 vs. 24.2% (p < 0.001); in HR-negative tumors, the numerical difference was not significant (27.2 vs. 36.4%; p = 0.125) [64]. Due to the lack of immediate clinical consequences, there is currently no AGO recommendation for *PIK3CA* mutation analysis before NACT (AGO+/-).

In early TNBC, germline *BRCA* (*gBRCA*) status is predictive of response to NACT. In the neoadjuvant GeparQuinto trial, in 74 (15.8%) out of 469 TNBC patients with available germline DNA, *BRCA1* (n = 61) or *BRCA2* (n = 13) mutations were detected. pCR (ypT0/ypN0) was observed in 50% (n = 37) of the mutation carriers but in only 31.1% (n = 123) of patients without mutations (p = 0.002). In patients without *BRCA* mutations (hazard ratio (HR) = 0.20; 95% confidence interval (CI) 0.11–0.34; p < 0.001) but not in mutation carriers (HR = 0.48; 95% CI 0.18–1.27; p = 0.129), pCR (ypT0/ypN0) was significantly correlated with DFS [65]. As there are evidence-based consequences for patient management beyond the neoadjuvant setting, *gBRCA* determination is recommended in TNBC (LoE II/B/AGO+). Yet, as shown earlier in the GeparSixto trial, the use of platinum compounds should not depend on the *gBRCA* status.

In patients with NACT, detection of > 1 circulating tumor cell (CTC) is an independent prognostic factor for locoregional relapse-free (HR = 1.8; 1.2–2.7; p = 0.001) survival, distant DFS (HR = 2.4; 1.9–3.1; p < 0.0001), and OS (HR = 2.6; 1.9–3.4; p < 0.0001). CTC positivity was not correlated with pCR in this meta-analysis

comprising 2,156 patients from 21 studies [66]. Despite the high LoE (I Ba), AGO does not recommend CTC detection in clinical routine due to the lack of therapeutic consequences (AGO+/-).

## Neoadjuvant Chemotherapy

Survival rates are similar after primary systemic ('preoperative', 'neoadjuvant') chemotherapy (NACT) and adjuvant therapy [67]. pCR defined as ypT0 ypN0 or ypT0/is ypN0 is associated with improved survival [68, 69]. NACT is the preferred therapeutic option in patients who have a clear indication for adjuvant postoperative chemotherapy (LoE 1/B/AGO+). In particular, in patient subgroups where a pCR is strongly associated with improved survival such as in TNBC, HER2-positive, and luminal B-like (HR-positive/HER2-negative/grade 3, high KI 67) cancer, NACT (plus targeted therapy) should be the preferred therapeutic approach (AGO++). In patients with TNBC (regardless of *gBRCA1/2* mutation status or positive family history for breast or ovarian cancer), a platinum-containing regimen may be considered (LoE 2b/B/AGO+) based on data from phase II randomized trials (e.g. GeparSixto, CALGB 40603) [70, 71]. The addition of carboplatin was not only associated with an increased pCR rate in both neoadjuvant trials, but also resulted in a significant improvement in GeparSixto with a DFS rate of 85.8% (with carboplatin) vs. 76.1% without carboplatin (HR 0.56;  $p = 0.0350$ ) and a clinically meaningful albeit statistically not significant improvement in DFS (absolute 5%) in the CALGB 40603 study. Furthermore, the results of the GeparSepto trial suggest particular benefit from using nab-paclitaxel 125 mg<sup>2</sup> weekly instead of paclitaxel for patients with TNBC, which was not observed in the ETNA trial (LoE 2b/B/AGO+/-) [72]. For HER2-positive patients, HER2-directed therapy is standard as part of neoadjuvant therapy. Given the significant increase in pCR rates and trend for improved progression-free survival observed in the neoadjuvant NeoSphere trial with the addition of pertuzumab to trastuzumab, dual blockade is highly recommended [73, 74] (LoE 2b/B/AGO++). With respect to endocrine neoadjuvant therapy, in exceptional situations, endocrine treatment with gonadotropin-releasing hormone (GnRH) analogues plus an AI may be considered for premenopausal women (LoE 1b/C/AGO+/-).

Response-guided treatment has been shown to be beneficial within the GeparTrio trial. Consequently, in the case of response after 2 cycles of DAC (docetaxel, adriamycin, cyclophosphamide) in HR-positive breast cancer, a total of 8 instead of 6 cycles of DAC may be considered to be appropriate (LoE 2b/C/AGO+). In the case of no response after 2 cycles of DAC, continuation of NACT with a non-cross-resistant regimen (LoE 2b/B/AGO+) such as 4× vinorelbine/capecitabine (LoE 1b/B/AGO+) may be beneficial [75]. This can be an option in individual cases but cannot be considered as a routine approach.

Post-neoadjuvant concepts are currently being investigated in clinical trials, and trial participation is recommended if possible, particularly in the case of no pCR. There is at present no indication for further chemotherapy in the case of no pCR outside of con-

trolled trials. Given the positive results of the CREATE-X study, capecitabine might be an option in individual patients with TNBC and without pCR (LoE 2b<sup>a</sup>/B/AGO+/-), but these data are not yet published.

Novel predictive factors, such as tumor-infiltrating lymphocytes (LoE I/B/AGO+), or phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutation in the tumor (LoE II/B/AGO+/-), are promising tools but currently not recommended in the routine clinical setting [76–79]. Patients with *gBRCA* mutations have a higher probability to achieve a pCR [80].

The indications for mastectomy after NACT remain unchanged: positive margins after repeated excisions (LoE 3b/C/AGO++), lack of feasibility of radiotherapy (LoE 5/D/AGO++), and presence of inflammatory breast cancer (with no more than clinical complete response, LoE 2b/C/AGO+). In inflammatory breast cancer with pCR after NACT, BCT may be discussed with the patient. Furthermore, large tumors (cT4a-c) at first diagnosis represent only a relative indication for mastectomy after NACT (LoE 2b/B/AGO+/-). In the case of nodal involvement, clip marking of the positive nodes is recommended if possible (LoE 5/D/AGO+). The sentinel lymph node (SLN) procedure is recommended preferably after neoadjuvant therapy in the case of cN0 (LoE 2b/B/AGO+), see also chapter on surgery [81–84].

## Breast Cancer Surgery under Oncological Aspects

The extent of breast surgery has been clearly defined in recent years. No ink on tumor is the widely accepted standard for patients who undergo primary surgery as well as for patients who are treated with primary systemic treatment (provided that all suspicious lesions according to preoperative imaging are resected (LoE 2a/A/AGO++ and LoE 3b/C/AGO+, respectively)

Although the role of axillary staging is increasingly questioned especially in subsets of patients whose adjuvant systemic treatment is already defined by the intrinsic subtype of the tumor, AGO clearly states that SLNB remains the standard of care for patients with invasive disease (LoE 1b/A/AGO++). Participation in the INSEMA trial is recommended. Axillary dissection (AD) as a staging procedure has been deleted in the 2017 guidelines (LoE 3/A/AGO-).

In patients with 1–2 positive SLNs who undergo BCT and irradiation of the breast, completion of AD is being more and more abandoned in clinical practice. The ACOSOG Z0011 trial presented 10-year follow-up data at ASCO 2016. Only 1 additional axillary recurrence was observed in the SLNB arm (compared to the 5-year report). The overall regional recurrences after 10 years were 2 (0.5%) in patients who underwent AD and 5 (1.5%) in patients who underwent SLNB alone [85].

Due to limitations of the ACOSOG Z0011 trial and the lack of conformational studies, AGO did not change the recommendation grade for AD in these patients (LoE 1b/B/AGO+/-) but recommends the participation in ongoing trials (INSEMA, SENOMAC).

The role of SLNB in the neoadjuvant setting has been a matter of intense debate in recent years. Many clinicians agree that axillary staging after NACT would be more beneficial for the patient (reduction to one-step surgery, reduction of the AD rate due to conversion from N1 to N0, determination of pCR as a new important prognostic parameter). However, data on the feasibility and reliability of SLNB in this setting were controversial, and no data on regional recurrences are available.

The French GANEA II study, a prospective multicenter cohort study, examined 418 clinically node-negative patients who underwent SLNB alone after NACT. The detection rate for the SLN was 97%. Only 1 (0.2%) axillary recurrence was observed after 3 years [86]. In a retrospective unicentric study, Galimberti [87] published similar results. After 5 years of follow-up, only 1 (0.6%) axillary recurrence was observed in clinically node-negative patients who underwent SLNB after NACT.

In view of these data, AGO modified the recommendations from 2016 and recommends SLNB after NACT in cN0 patients (LoE 2b/B/AGO+). SLNB before NACT remains an option if an impact on adjuvant treatment decisions is expected (LoE 2b/B/AGO+/-).

For patients who present initially with (histologically proven) positive axillary lymph nodes (pN1), the feasibility and accuracy of SLNB is clearly restricted (SENTINA, ACOSOG 1071, GANEA I) [88–90]. Data on long-term outcome are insufficient, and it is unclear if the unfavorable FNR translate into higher rates of recurrences. Therefore, AGO cannot generally recommend SLNB as standard procedure in clinically negative axillae after NACT (ycN0) in cases of pre-NACT histologically proven tumor-infiltrated lymph nodes (cN+/pN+) (LoE 2bB/AGO+/-). AD may be the safer alternative in such cases (LoE 2b/B/AGO+).

Suggestions have been provided to improve the FNR for patients who convert from cN1 to cN0 under NACT. The 2017 AGO recommendations defined a clear LoE and recommendation grade for these proposals. None of the procedures is, however, recommended for routine clinical practice since insufficient outcome data are available for these patients.

An unplanned retrospective analysis of the ACOSOG Z1071 revealed that the FNR could be improved when more than 2 SLNs were removed or when a dual tracer technique was applied. More than 2 SLNs were, however, identified in only 43.1% of the patients in the ACOSOG study and in 34% in the SENTINA trial [90]. The recommendation of removing more than 2 SLNs would therefore be applicable in only an insufficiently small cohort of patients. It could furthermore motivate surgeons to remove additional non-SLNs and thus perform an undirected sampling (LoE 3b/C/AGO+/-).

The improvement of the FNR by use of a dual tracer technique was not confirmed in the multivariate analysis of the SENTINA trial. Patients with a dual tracer had significantly more lymph nodes removed (3 vs. 2). The FNR was not significantly associated with the tracer technique [90] (LoE 3b/C/AGO+/-).

The prospective French FNAC study showed a significant correlation between the size of the lymph node metastases (defined as pN1) and the FNR. When only patients with macrometastases

were considered pN1, the FNR was 16.9%. When micrometastases (pN1 (mi)) or isolated tumor cells (pN0 (i+)) were considered as positive, the FNR dropped to 13.3 and 8.4%, respectively [91] (LoE 2b/B/AGO+/-).

In 2016, Caudle et al. [92] presented data from a new technique, the targeted axillary dissection (TAD). With the combined use of SLNB and a targeted removal of the biopsy-proven positive lymph node marked with a clip at the time of diagnosis, the FNR was as low as 1.4% in this series. Many issues including the surgical technique, the reproducibility of this retrospective unicenter study, and the extent of surgery are still unclear. Further studies focusing on these issues are certainly required before this procedure is introduced into routine clinical use (LoE 3b/C/AGO+/-).

### Oncoplastic and Reconstructive Surgery

Oncoplastic surgery is defined as the use of plastic surgical techniques at the time of tumor excision to enable safe resection margins and to preserve an aesthetic breast contour. Oncoplastic surgery increases the number of BCT, enables the resection of larger tumors, reduces the number of re-excisions, and leads to high patient satisfaction. Local recurrence rates are the same as in classical BCT [93]. The oncological safety of oncoplastic surgery is comparable to BCT [94].

If BCT is not feasible, breast reconstruction with breast implants, free or pedicled autologous tissue transfer reconstruction, or autologous tissue transfer combined with implants should be offered (LoE B/AGO+). Indications for the various techniques must be weighed up carefully depending on patient and tumor parameters. In mastectomy, preservation of the nipple-areola complex may be performed (LoE 2b/B/AGO++). The best implant reconstruction (IR) results will be achieved if no locoregional irradiation is necessary (LoE A/AGO++). In the case of a need for radiotherapy, IR prior to radiotherapy is preferable (LoE 2a/AGO+) as compared to IR following mastectomy and radiotherapy (LoE B/AGO+/-). Nevertheless, increased complication rates like capsular contraction, necrosis, or infections in at least 20–40% of cases are described.

If autologous reconstruction is planned (e.g. TRAM, DIEP), radiotherapy should be performed prior to reconstructive surgery in order to avoid higher rates of fibrosis and necrosis and poorer aesthetic results (LoE 2/AGO+) [95, 96].

The use of lipotransfer is an increasingly employed additional tool to refine breast-reconstructive surgery with so far no data suggesting an increased risk of disease recurrence. Lipotransfer can be performed after mastectomy and IR (LoE 2a/B/AGO+). After BCS, lipotransfer should be performed on an individual basis and after detailed informed consent (LoE 2a/B/AGO+) [97].

If IR is not suitable, the preferred pedicled flap, e.g. TRAM (LoE 2a/AGO+), or the free tissue flap, e.g. DIEP (LoE 2a/AGO+), may be considered [98].

For prophylactic mastectomy without *BRCA* mutation, an individual decision depending on personal/family history and mutational status for new high- and moderate-risk genes is necessary.



## Adjuvant Radiotherapy

Adjuvant radiotherapy is an essential part of the primary treatment in early breast cancer and contributes substantially to improve survival. However, breast cancer specialists sometimes disagree with regard to the interpretation of the current data and the standard of care. Therefore, experts from the field of gynecology and radiotherapy representing their corresponding guideline committees, AGO and *Deutsche Gesellschaft für Radioonkologie* (German Society of Radiation Oncology, DEGRO), developed the joint AGO recommendations for adjuvant radiotherapy based on an intense consensus discussion. Disagreement on those statements is highlighted. For technical details on radiotherapy, we agreed to refer to the corresponding updated DEGRO practical guidelines 2014 [99, 100].

The AGO and DEGRO experts agreed with regard to future developments in radiotherapy: In many situations, radiotherapy will be optimized, reduced, or even spared. On the other hand, use of radiotherapy may be established for indications that were not considered before.

The type of breast irradiation after BCT is still a matter of debate. After the convincing data of the START B trial, hypofractionated irradiation that consists of 15 or 16 fractions to total doses of 40–42 Gy is widely accepted as the new standard of breast radiotherapy according to international guidelines [101–104] and common practice [105–108] and was recently confirmed by an updated Cochrane analysis. We agreed to underscore hypofractionated irradiation (15–16 fractions) as the preferred type of irradiation and to leave conventional radiotherapy as an alternative method. In patients < 50 years of age and in high-risk patients aged  $\geq$  50 years, an additional boost of 10–16 Gy to the tumor bed is recommended although the improvement in local control is quite small in patients older than 40 years [109].

If radiotherapy of the regional lymph nodes is included, conventionally fractionated radiotherapy (25–28 fractions) is still recommended.

In patients with a life expectancy of below 10 years, omission of radiotherapy is an option particularly for patients with a low risk of recurrence such as pT1 pN0 G1–2, HR-positive/HER2-negative if adjuvant endocrine treatment is performed (LoE 1a/B/AGO+) [110]. There is no influence on OS, and side effects can be avoided. AGO and DEGRO agree that in patients > 70 years, intraoperative accelerated partial breast irradiation (APBI) can be delivered as the sole radiotherapy modality (intraoperative radiation therapy (IORT) 50 kV, intraoperative electron radiation therapy (IOERT); only for pT1 pN0 R0 G1–2, HR-positive, non-lobular, no extensive DCIS, IORT during first surgery).

Irradiation of the chest wall (postmastectomy radiotherapy, PMRT) is indicated if more than 3 axillary lymph nodes were tumor-infiltrated [111]. With regard to patients with 1–3 infiltrated nodes (pN1), we recommend PMRT for any number of positive lymph nodes in all high-risk patients and in selected patients with intermediate risk. However, retrospective analyses suggest that in low-risk patients with less than 4 tumor-infiltrated lymph nodes (pN1a), in some cases, no real benefit can be expected, e.g. in those

with ER-positive, HER2-negative, well differentiated (G1) pT1 tumors [112]. On the other hand, in patients with high-risk features, e.g. high axillary tumor load (i.e. > 25% of removed lymph nodes are positive), undifferentiated (G3) tumors, triple-negative immunohistochemistry, lymphovascular invasion, or in younger patients with ER-negative tumors (< 45 years) or HER2-positive tumors (< 40 years), several analyses show an elevated risk of recurrence and consequently an indication for PMRT [113, 114].

Based on retrospective data, omission of PMRT was discussed in patients with pN1 tumors if 3 of 4 low-risk criteria are fulfilled (ER-positive, G1, HER2-negative, pT1) [115]; on the other hand, in patients with high-risk criteria such as vessel invasion, HER2-positivity, high grade (G3), high proportion of positive lymph nodes (> 25%), and young age (< 40 or < 45 years if ER-negative or medial tumor location), a benefit from PMRT is expected [113, 114]. However, for some patients, individual discussion will be required.

Radiotherapy of the medial supra/infraclavicular and internal mammary chain lymph nodes consistently improved DFS and distant metastasis-free survival in 2 large randomized controlled trials [116, 117] and a Danish population-based study [118] resulting in a small but statistically significant OS benefit in the meta-analyses of these trials [119]. The majority of patients in these trials had either node-positive breast cancer or centrally or medially located node-negative breast cancer. AGO and DEGRO experts recommend lymph node irradiation of the internal mammary chain according to tumor location, number of lymph nodes involved, and tumor biology:

Radiation of the thoracic wall and regional lymph nodes except the axillary lymph nodes is recommended in patients aged > 45 years with more than 25% of involved lymph nodes, or < 45 years and ER-negative or medial tumor, or < 40 years, HER2 overexpressed or pL1 or G3 or TNBC. For patients who received trastuzumab, radiotherapy of the mammary chain lymph nodes is not recommended.

## Adjuvant Endocrine Therapy

In the adjuvant situation, endocrine therapy is indicated in all patients with HR-positive breast cancer and should also be considered in cases with low receptor levels ( $\geq$  1–9%; LoE 1/A/AGO++). If chemotherapy is being administered, endocrine therapy starts after cytotoxic therapy. Endocrine adjuvant therapy is defined as ‘initial therapy’ (years 0–5) and ‘extended adjuvant therapy’ (EAT, years 6–15; AGO++). A treatment duration of 5 years is standard of care. Whether or not EAT is indicated, should be based on individual risk/benefit considerations.

In premenopausal and perimenopausal patients, treatment with tamoxifen might be offered for 5–10 years (LoE 1a/A/AGO++). In accordance with data from the ATLAS and ATTOM studies, tamoxifen therapy can be extended to up to 10 years [120]. If the patient is postmenopausal after the initial 5 years of endocrine therapy, according to the data from the MA 17 study, endocrine therapy can be continued after 5 years of tamoxifen with 2.5–5 years of letrozole (LoE 1b/B/AGO+) [121].



If ovarian function has been restored within the first 8 months after chemotherapy, treatment with a GnRH analogue plus tamoxifen or in combination with the AI exemestane for 5 years can be considered on an individual risk basis (LoE 1b/B/AGO+/-). If the patient is younger than 35 years, according to the SOFT study, a combination of tamoxifen with a GnRH analogue can be recommended (LoE 1b/B/AGO+) [122]. However, increased side effects may impair compliance. In view of the numerous treatment options available, as well as different possible sequences, adjuvant treatment recommendations for postmenopausal patients are challenging.

For the initial endocrine therapy (years 0–5), there has been extensive discussion regarding the use of tamoxifen in comparison with an AI or the sequential use of tamoxifen and an AI. 2 meta-analyses have been published during the last year that both confirm that AIs are preferable in comparison with tamoxifen for 5 years [123, 124]. In the Early Breast Cancer Trialists' meta-analysis, 5 years of treatment with an AI led not only to an improved 10-year breast cancer mortality rate in comparison with 5 years of tamoxifen, but also to a reduced rate of recurrences. Sequential treatment with tamoxifen followed by an AI was also superior with regard to mortality, so that in postmenopausal patients either an AI or sequential treatment with tamoxifen followed by an AI, or vice versa, should be used (LoE 1a/A/AGO++). The 5-year AI therapy is preferable, particularly in patients with lobular cancer or with a high risk of recurrence.

The issue of whether EAT should be recommended for recurrence-free patients after the initial adjuvant therapy of 5 years is complex. There are still no validated biomarkers that are capable of identifying patients who are at risk of late relapse or that can help select patients for extended therapy versus a shorter period of treatment.

After 2–5 years of tamoxifen therapy in patients with higher risk, extended therapy with 5 years of tamoxifen can be administered on the basis of the ATLAS study (LoE 1a/A/AGO++), or 2.5–5 years of AI treatment in accordance with the MA 17 study (LoE 1a/B/AGO++) [125, 126].

The data on extending AI-containing initial therapy beyond 5 years is currently heterogeneous. While 2 studies have shown a benefit (MA 17R: 5 years of AI after 5 years of AI, with or without prior therapy with tamoxifen; LATER: 5 years of AI after 4 years of endocrine therapy, 11.7% were pre-treated with AI and 36.9% with tamoxifen followed by AI) [127, 128], 3 studies presented at the 2016 San Antonio Breast Cancer Symposium were negative for the overall population (DATA, IDEAL, and NSABP B-42). However, since some subgroups may benefit, extension of endocrine therapy with an AI should be offered after the initial AI-containing therapy in patients who are at higher risk and have tolerated the AI well, e.g. those with good bone health, younger age, high risk according to immunohistochemical characteristics, and positive nodal status (LoE 1b/B/AGO+). However, there is as yet no evidence of a significant effect on OS. In patients who are at low individual risk and/or have poor tolerance for the AI, AI therapy should not be continued beyond 5 years (LoE 1b/B/AGO-).

## Adjuvant Cytotoxic and Targeted Therapy

If adjuvant chemotherapy is indicated, neoadjuvant therapy should always be considered (AGO++). In adjuvant therapy, systemic treatment encompassing 6 cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide) is no longer recommended. A comparison of regimens using 4 cycles of doxorubicin and cyclophosphamide (AC) with 6 cycles of FEC in the framework of NSABP B-36 showed no differences in either DFS or OS after a median follow-up period of 82.8 months ( $p = 0.74$  and  $0.65$ , respectively) [129]. An analysis of HR status also showed no advantage for 6 cycles of FEC. However, the side effects with FEC were much more severe, and more deaths occurred as compared to 4 cycles of AC ( $n = 5$  vs.  $2$ ).

Standard adjuvant chemotherapy consists of combination regimens based on anthracyclines and taxanes in patients with HER2-negative tumors (LoE 1a/A/AGO++). Treatments of choice include  $4 \times$  EC/AC, followed by  $12 \times$  paclitaxel (weekly, q7d), or  $4 \times$  docetaxel (q21d), or treatment with  $6 \times$  DAC (AGO++). The benefit of these combinations has recently been confirmed with the publication of the 10-year data from E1199 [130]. Here, regimens with docetaxel 3-weekly ( $100 \text{ mg/m}^2$  body surface area q21d), docetaxel weekly ( $35 \text{ mg/m}^2$  q7d), paclitaxel 3-weekly ( $175 \text{ mg/m}^2$  q21d), or weekly paclitaxel ( $80 \text{ mg/m}^2$  q7d) were compared after 4 cycles of AC. The study population was enriched with patients carrying high-risk features (46% premenopausal, only 12% with negative nodal status). There were significant advantages for paclitaxel weekly and docetaxel given every 3 weeks regarding DFS but not OS (DFS  $p < 0.001$ , OS  $p = 0.07$ ). Therefore, particularly 3-weekly docetaxel was found to be more effective than 3-weekly paclitaxel (DFS: HR = 0.79; 95% CI 0.68–0.90; OS: HR = 0.86; 95% CI 0.73–1.00), and weekly paclitaxel was more effective than 3-weekly paclitaxel (DFS: HR = 0.84; 95% CI 0.73–0.96; OS: HR = 0.87; 95% CI 0.75–1.02). Of particular interest was the subgroup with TNBC: after 4 cycles of AC, paclitaxel weekly showed a significant OS benefit in comparison with 3-weekly paclitaxel (HR = 0.69; 95% CI 0.50–0.94). This treatment should be considered in patients with TNBC.

If comorbidities forbid the use of anthracyclines, treatment with docetaxel and cyclophosphamide might be used as an alternative regimen (LoE 1b/B/AGO+). In individual cases, treatments using paclitaxel mono weekly (LoE 1b/B/AGO+/-) or CMF (cyclophosphamide, methotrexate, fluorouracil) (LoE 1a/A/AGO+/-) may also be considered [131, 132].

In the case of a high tumor burden, e.g. with 4 or more affected lymph nodes, dose-dense and dose-escalated treatment with epirubicin followed by paclitaxel followed by cyclophosphamide, q14d, should be considered instead of standard regimens. At present, platinum agents cannot be recommended in the adjuvant setting due to a lack of data and should be considered in individual cases only (LoE 5/D/AGO+). This is in contrast to the recommendations pertaining to the neoadjuvant setting (see above).

In HER2-positive disease, a combination of trastuzumab and a taxane starting simultaneously is recommended. The optimal du-

ration is 1 year (LoE 1b/A/AGO++) [133]. In individual cases, e.g. when comorbidities or side effects inhibit longer treatment duration, treatment for 6 months may be considered (LoE 1b/A/AGO+/-). It has to be acknowledged, however, that the PHARE trial analyzing this regimen did not beyond doubt demonstrate non-inferiority of the shorter regimen compared to the 1-year regimen [134]. Alternative anthracycline-free combination partners for trastuzumab are docetaxel and carboplatin (LoE 1b/A/AGO+) or in individual cases, e.g. in patients with tumors < 3 cm and negative nodal status, treatment with 12× paclitaxel q7d (LoE 2b<sup>a</sup>/B/AGO+/-). It has to be acknowledged, however, that in the APT trial evaluating this regimen, a tumor size of 3 cm did represent an inclusion criterion; nevertheless only about 5% of patients presented with a tumor size of 2–3 cm [135]. With regard to alternative anti-HER2 treatments, neither lapatinib nor dual therapy with lapatinib plus trastuzumab can currently be recommended (LoE 1b<sup>a</sup>/B/AGO-). The results of the ALTTO study showed no advantage with regard to DFS or OS either for sequential trastuzumab and lapatinib or for the combination [136]. However, in the subgroup of HR-negative patients, a trend towards improved DFS was observed for the combination (HR = 0.82; 95% CI 0.65–1.04). It is possible that this group may benefit, but the current data is insufficient for a recommendation. With regard to dual therapy using trastuzumab plus pertuzumab, an evaluation of ongoing studies is awaited.

## Gynecological Issues in Breast Cancer Patients/ Contraception

### *Treatment of Menopausal Symptoms*

Classical hormonal therapy to alleviate menopausal symptoms is not indicated in breast cancer patients, particularly in ER-positive disease (LoE 1b/B/AGO-) but might be considered in individual cases and after failure of other non-hormonal treatments (LoE 2a/B/AGO+/-). Tibolone is contraindicated [137] (LoE 1b/A/AGO-/-), while topical vaginal application of estriol may be used for urogenital symptoms [138] (LoE 4/D/AGO+/-). Menopausal symptoms such as hot flushes, night sweats, or sleep disturbances may be treated with various non-hormonal remedies, e.g. serotonin reuptake inhibitors (i.e. venlafaxine (LoE 1a/A/AGO+) or gabapentin (LoE 1a/A/AGO+), which carry the potential to reduce hot flushes by about 60% [139].

The majority of studies on the efficacy of herbal treatments for menopausal symptoms – mostly hot flushes – were not conducted in women with breast cancer, and many were of short duration [140]. Increased pharmacovigilance for herbal medicines is required, e.g. initiatives to stimulate reporting of suspected adverse reactions. Neither flax seed [141] nor black cohosh (*Cimicifuga racemosa*) [142] nor St. John's wort [143] nor ginseng root [144] could improve menopausal symptoms.

Five randomized controlled trials reported on the efficacy of soy for hot flushes, showing no significant reduction in hot flushes compared to placebo (LoE 1b/B/AGO-). There is a lack of evidence showing harm from use of soy with respect to risk of breast cancer

or recurrence based on long-term observational data. Soy intake consistent with that of a traditional Japanese diet (2–3 servings daily, containing 25–50 mg isoflavones) may be protective against breast cancer and recurrence. Human trials show that soy does not increase circulating E2 or affect estrogen-responsive target tissues. Prospective data of soy use in women while on tamoxifen does not indicate an increased risk of recurrence. While there is no clear evidence of harm, better evidence confirming safety is required before the use of high-dose (≥ 100 mg) isoflavones can be recommended for breast cancer patients [145].

A systematic review and meta-analysis of 11 randomized controlled trials showed that red clover had a positive effect on alleviating hot flushes in menopausal women (LoE 1b/B/AGO+/-). Slight changes were found in follicle-stimulating hormone (FSH), luteinizing hormone, testosterone, and sex hormone-binding globulin levels. More importantly, a significant effect of red clover consumption on the estrogen status was noted. Furthermore, red clover may increase the risk of estrogen-dependent cancers as E2 showed a borderline increase in the red clover groups in comparison with controls based on 3 trials [146].

Physical exercise and cognitive behavioral therapy have positive effects on menopausal symptoms and, to a lesser degree, on the sexuality and physical functioning of patients with breast cancer experiencing treatment-induced menopause (LoE 1b/B/AGO+) [147].

Mind-body medicine (MBM; relaxation training, yoga, hypnosis) is reported to result in a moderate and even significant improvement in hot flushes scores, joint pain, fatigue, sleep, mood, and relaxation (LoE 1b/B/AGO+/+) [148]. These effects are seen even after longer periods of application and some months after stopping MBM. Acupuncture can also be used for hot flushes (LoE 1b/B/AGO+) and has shown moderate effects on depression (LoE 2b/B/AGO+/-).

### *Fertility Preservation*

Counseling on fertility preservation is suggested in all patients who wish to retain their fertility (LoE 4/C/AGO+). Application of GnRH analogues given 2 weeks prior to chemotherapy has been shown to give a higher rate of recovery of ovarian function after 2 years. However, in multivariable analysis, GnRH treatment was not an independent predictor of ovarian reserve indicating preservation of fertility [149] (LoE 1a/B/AGO+/-).

Menstrual history is reliable only in women under 45 years of age. A more precise evaluation of the ovarian reserve (particularly in perimenopausal patients) may be obtained by the measurement of FSH and E2 levels in the peripheral blood. Low anti-Muellerian hormone levels seem to be indicative of reduced ovarian reserve and chemotherapy-related amenorrhea in chemotherapy-treated breast cancer patients. An antral follicle count, defined as the sum of the follicle diameters of all follicles of 10 mm in both ovaries, can be easily performed at little extra cost (LoE 3b/B/AGO+/-) [150].

### *Contraception*

All patients of childbearing potential must be counseled about adequate contraception prior to systemic therapy [151], since cyto-

toxic treatment, including endocrine therapy, by itself does not confer reliable protection against pregnancy. The majority of contraceptive measures have not been tested in women after breast cancer.

### *Sexual Health*

Sexual complaints are common in breast cancer patients. They include sexual desire disorder/decreased libido (23–64% of patients), arousal or lubrication concerns (20–48% of patients), orgasmic concerns (16–36% of patients), and dyspareunia (35–38% of patients), and should be assessed. Screening tools may help physicians to address sexual health issues (LoE 4/C/AGO+) [152]. Non-hormonal lubricants and moisturizers are the primary treatment for vaginal dryness. Silicone-based products may last longer than water-based or glycerin-based products (LoE 1b/B/AGO+). For sexual health, interventions such as brief psychoeducational support, group therapy, sexual counseling, marriage counseling, or intensive psychotherapy have shown to be effective (LoE 1b/B/AGO+).

### **Complementary Therapy – Survivorship**

Complementary and alternative medicine (CAM) treatments are scrutinized under 2 separate aspects: i) Improvement or amelioration of side effects of conventional treatment, and ii) Improvement of cancer-related outcome.

Although many patients use CAM during cancer treatment or thereafter, existing data from randomized clinical trials are insufficient. This may be the result of the impossibility to perform randomized trials (e.g. smoking cessation, alcohol intake, going on a diet), a lot of bias (e.g. smoking and nutrition are related to socioeconomic status), and different lifestyle factors. Otherwise, traditional herbal medicines are mostly examined in Asia where they are a part of normal life (e.g. soy, ginseng, green tea). Certain CAMs are only regionally distributed.

Many herbs (e.g. Ginseng, Curcumin), enzymes (e.g. thymic peptides, proteolytic enzymes, L-carnitine), antioxidant supplements (e.g. selenium, co-enzyme Q 10), vitamins (e.g. A, E), traditional Chinese herbal medicine, and oxygen and ozone therapy have been investigated in relation to reduced side effects of cancer treatment or improved survival. In sum, there are no convincing data regarding improvement of side effects or survival, so that the AGO recommendations are mostly ‘+/-’. Otherwise, it is important to note that drug interactions may occur between CAM and anti-cancer treatments that can potentially reduce the activity of the anti-cancer treatment.

Acupuncture is effective in improving chemotherapy-induced nausea and vomiting (LoE 1a/B/AGO+), whereas no distinct effects on cognitive dysfunction, fatigue, pain, leucopenia, and chemotherapy-induced polyneuropathy exist [153].

Acknowledging the need of patients to contribute to the treatment of their breast cancer, the cessation of cigarette smoking and reduction in alcohol intake have been emphasized as possible

measures, although there are no data from randomized trials [154]. Nevertheless, the AGO recommend this approach (LoE 1b/B/AGO-). Furthermore, the necessity to adhere to a healthy nutritional and dietary concept according to recognized recommendations is emphasized. Overall, a reduction in fat intake is justified with regard to various health aspects and is therefore recommended. Reduced fat intake is linked to disease-specific as well as general health effects by a reduction in obesity which has clearly been demonstrated to improve OS and DFS [155]. More specifically, newer data suggests that high-fat dairy products should be avoided. Mindfulness-based stress reduction is an 8-week program aiming at developing participants’ coping resources and mindful awareness. The program consists of guided meditation, guided body scan (a specific awareness exercise) and meditation, and yoga. Psychoeducation tackles stress and stress reactions [156]. Yoga improves sleep, quality of life, stress, anxiety, depression, and fatigue (LoE 1b/B/AGO+), whereas the beneficial effects of Qi Gong or Tai Chi are not so clear [157]. In summary, the best way to improve mental and physical health during/after breast cancer treatment is to avoid negative lifestyle factors, engage in healthy nutrition and physical exercise, and maintain a normal body weight (AGO++).

### **Breast Cancer: Special Situations**

Breast cancer in young women (< 35 years) or during pregnancy always is a challenging clinical situation, and a detailed consensus was recently published [158]. There is growing evidence that GnRH should be used for ovarian protection during chemotherapy in these patients (LoE 1b/AB/AGO+) [159]. Furthermore, early counseling for contraception is strongly advised (LoE 2b/B/AGO++) [160]. Breast cancer patients who are pregnant or breastfeeding should be treated with great care. However, diagnostic procedures, surgery, as well as medical treatment should be performed like in non-pregnant patients with specific attention to the week of gestation (LoE 2b/B/AGO+). Staging should only be carried out if indicated. However, bone scans should be done post delivery. Recommendations regarding male and elderly patients or inflammatory breast cancer have not changed in 2017.

In a typical case of axillary cancer of unknown primary (axillary CUP), histopathology will show characteristic features of occult breast cancer, such as ER+/PR+/GATA+ immunophenotype (LoE 5/D/AGO++). In other situations, e.g. in the case of metastatic TNBC or unusual morphology, non-breast malignancies should be excluded by clinical examination and imaging techniques [161] and/or immunohistology [162] (LoE 5/D/AGO++). In axillary CUP, the usefulness of molecular techniques for defining the site of origin, such as gene expression profiling, epigenetics, or panel sequencing, is not well established but may help in selected patients (LoE 2c/B/AGO+/-) [163–165]. A PET/PET-CT (positron emission tomography/computed tomography) should be performed [166] (LoE 3b/B/AGO+). In the case of occult breast cancer, (neo-) adjuvant systemic therapy according to breast cancer guidelines (AGO) is recommended (LoE 5/D/AGO++).



A new recommendation concerning Paget's disease of the nipple is to use immunohistology (ER, PR, HER2, CK7) to differentiate benign and HER2-negative cases from typical HER2-positive cases (LoE 5/D/AGO++) [167]. HER2-negative Paget's disease of the nipple is more often limited to the nipple-areola complex (NAC), and with these cases, surgical resection only without adjuvant radiotherapy is recommended (LoE 4/D/AGO++), and SLNB is discouraged (LoE 2/B/AGO-).

For phyllodes tumors, a consensus review on the diagnosis and treatment was published in 2016 [168]. Complete surgical resection (R0 resection) is the mainstay of therapy (LoE 2/B/AGO++), but the definition of an appropriate surgical margin is not clear. Adequate resection is important especially in malignant phyllodes tumors, as they are associated with a recurrence rate of 29.6%, with metastases and death being observed in 22% [169]. The role of radiotherapy in the treatment of malignant phyllodes tumors is not clear, and postoperative radiotherapy did not impact cancer-specific survival in multivariate analysis [170]. However, in a recent meta-analysis, patients that were treated with postoperative radiotherapy had a lower relative risk of local recurrence than those not receiving postoperative radiotherapy, even after margin-negative wide local excision [171]. A similar effect on local recurrence has been described in an analysis of the SEER database [172]. AGO is therefore undecided regarding its recommendation for radiotherapy in phyllodes tumors of T ≥ 2 cm (BCT) or T ≥ 10 cm (mastectomy) (LoE 2b/C/AGO+/-).

Primary and secondary angiosarcoma (angiosarcoma with or without a history of radiotherapy) are now discriminated in the AGO guidelines because of differences in clinical presentation (age, symptoms, imaging), therapeutic approaches, and prognosis [173]. Primary angiosarcoma typically presents as a large, ill-defined mass in the breast parenchyma of young patients, and BCT is discouraged (LoE 3a/C/AGO-). Secondary or radiation-induced angiosarcoma presentation includes purple cutaneous discoloration, eczematous rash, hematoma-like appearance, and breast swelling after BCT [174]. Secondary mastectomy is advocated (LoE 3a/C/AGO++) because of the very aggressive disease course [175]. Adjuvant radiotherapy in high-risk cases may improve tumor control following surgical resection even in the re-irradiation setting (LoE 2b/C/AGO+/-). In the case of distant metastases or unresectable tumors, treatment, including the use of chemotherapy, should be handled like in soft tissue sarcomas (LoE 4/C/AGO++).

Furthermore, we have added a new subsection on breast implant-associated anaplastic large-cell lymphoma (BIA-ALCL) which is a distinct type of T-cell lymphoma that arises around

breast implants, specifically in patients with textured implants (< 1/100,000 women with implants). The chief presenting symptom is late-onset seroma in two thirds of the cases or, less commonly, a mass lesion [176]. AGO recommendations for establishing a diagnosis of BIA-ALCL include sonography (for newly occurring seromas 1 year after implant placement, tumor mass) and effusion cytology. Upon confirmation of the diagnoses, breast MRI and further workup, including nodal status, PET-CT, bone marrow biopsy, as well as lymphoma subtyping and histological staging on resection specimens are recommended (LoE 5/D/AGO++) [177]. Treatment recommendations include implant removal, complete capsulectomy including tumor removal (LoE 3a/C/AGO++), and the removal of suspicious lymph nodes without routine SLNB (LoE 4/D/AGO++) or radiation (LoE 4/D/AGO+/-) should be considered. In Germany, reporting to the *Bundesinstitut für Arzneimittel und Medizinprodukte* (Federal Institute for Drugs and Medical Devices, BfArM) as a serious adverse event is obligatory according to §3 MPSV.

### Online Supplemental Material

**Suppl. table 1.** AGO grades of recommendation

**Suppl. fig. 1.** Pretherapeutic diagnostics of suspect lesions (BIRADS 4).

**Suppl. fig. 2.** Risk-reducing bilateral mastectomy in healthy women.

**Suppl. fig. 3.** Radiotherapy of other locoregional lymph drainage regions.

To access the supplemental material please refer to [www.karger.com/?DOI=477575](http://www.karger.com/?DOI=477575).

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### References

References can be found in the appendix; please refer to [www.karger.com/?DOI=477575](http://www.karger.com/?DOI=477575).