AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2016

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Introduction

For the last 15 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 valid-

ity (Oxford level of evidence (LoE), www.cebm.net) [1] and clinical relevance (AGO grades of recommendation, GR) (table 1). We herewith present the 2016 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.

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Table 1. AGO grades of recommendation

++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.
+	This investigation or therapeutic intervention is of limited benefit for patients and can be performed.
+/-	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge, a general recommendation cannot be given.
-	This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.
-/-	This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

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 regardless of age (LoE 3b/C/AGO +), particularly if an impact on treatment decisions is anticipated. The rate of *BRCA1/2* mutations, however, has been shown to decrease with increasing age in TNBC [6]. 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) allow further classification of most of these variants. Recent data suggest that no further high-risk genes such as *BRCA1/2* (odds ratio (OR) > 5.0) exist and that the remaining heritability is due to moderate-risk genes (e.g. *RAD51C*, *ATM*, *BRIP1*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *PTEN*; OR 1.5–5.0) and low-risk alleles (*FGFR2*, *TOX3*, *2q35*, *11q15*, *SLC4A7*, *5p12*, *MAP3K1*; OR < 1.5) that are transmitted via an oligo-genetic trait [7]. *RAD51C* and *PALB2* were recently described as moderate-to-high-risk genes [8]. 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 controlled clinical trials. Furthermore, clinical genetic testing for low-risk variants 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 intensified 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 recently presented data of the GeparSixto trial, the addition of carboplatin to neoadjuvant chemotherapy (NACT) is beneficial for patients with TNBC regardless of *BRCA1* or *BRCA2* mutation status. Overall, TNBC status in association with a *BRCA1* or *BRCA2* mutation displays 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 2ba/B/AGO +). The use of poly(ADP-ribose) polymerase (PARP) inhibitors is currently being validated in prospective randomized studies (LoE 2b/D/AGO +/-).

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 (stages I–IIA) offers the chance of surviving the disease with less treatment-induced impairment and better quality of life. 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, overdiagnosis, and overtreatment. Contrary to persistent criticism (mostly reflecting the complexity of data analysis), all available evidence confirms that mammography screening is capable of significantly reducing breast cancer mortality. Based on a recent review by Oeffinger et al. [9], the number needed to screen (NNS) to prevent 1 breast cancer death with a mortality reduction of 20% was estimated for women 40–49 years of age to be 1,770, for women 50–59 years of age 1,087, and for women 60–69 years of age 835, with regard to a 40% reduction, 753, 462, and 355 patients would need to be screened, respectively.

The limitations of mammography are well known, and new technologies to overcome these constraints are highly welcome. Within 2 randomized controlled trials (RCTs) and further cohort studies, digital breast tomosynthesis (DBT) proved to significantly increase both sensitivity and specificity, thus improving diagnostic accuracy. In the near future, DBT can be expected to replace standard 2D mammography for mammography screening [10–14]. At present, DBT can be recommended if further mammographic diagnostic tests like digital spot compression view are requested [15, 16] (LoE 2b/B/AGO +).

There is no data supporting a recommendation of breast ultrasound alone or automated breast volume scanning (ABVS) as breast cancer screening methods. A recent Cochrane Database systematic review from 2013 did not detect any controlled studies on the use of adjunct ultrasonography for screening of women with average breast cancer risk. 1 ongoing RCT was identified. The arguments against ultrasound as a sole screening modality are lack of reproducibility, high false-positive rate, low positive predictive value for biopsy, inability to detect ductal carcinoma in situ (DCIS) in most cases, operator dependency, and lack of quality assurance. Hence, there is presently no methodologically sound evidence justifying the routine use of ultrasonography as an adjunct screening tool in women with average breast cancer risk [17] (LoE 3b/C/AGO –).

Results of recently published cohort studies with automated whole-breast ultrasound examination (automated breast ultrasound (ABUS)/ABVS) promise to reduced physician examination time and operator dependence. Further research is, however, necessary to demonstrate equal accuracy to standard hand-held ultrasound examination [18–22] (LoE 3b/B/AGO +/-).

Elastography is an evolving new ultrasound-based imaging technology and has some advantages in diminishing the rate of Breast Imaging Report and Data System (BI-RADS) III lesions and in measuring the true size of breast cancer lesions. To further characterize focal breast lesions additionally to B-mode ultrasound in the differentiation of BIRADS 3- and BIRADS 4a masses, ultrasonographic elastography helps to decrease the false-positive biopsy rate [23, 24] (LoE 2a/B/AGO +).

Contrast-enhanced magnetic resonance imaging (MRI) plays an important role in diagnostic breast imaging in accepted indications as well as in high-risk patients. MRI should not generally be used

to assess symptoms or breast lesions. MRI may be used if clinical examination, mammography, and sonography do not yield a definitive diagnosis (LoE 2b/B/AGO +/-).

MRI should not generally be used for preoperative staging purposes in the case of BCT. According to a meta-analysis, the re-excision rate is not reduced but the initial and total rate of mastectomy is increased if a preoperative breast MRI is performed compared with no preoperative breast MRI. In the case of lobular invasive breast cancer, there is a significant reduction in the re-excision rate and no significant impact on the rate of mastectomies with the use of preoperative breast MRI. Furthermore, preoperative breast MRI does not reduce the rate of local recurrences and does not improve local recurrence-free survival and distant metastases-free survival [25–27]. This is why preoperative breast MRI is not recommended as a routine method for all patients. For some patients, e.g. with high breast density (American College of Radiology (ACR) 3–4), lobular invasive cancer, or suspicion for multilocular disease, it can be considered (LoE 1b/B/AGO +/-). MRI-guided vacuum biopsy is mandatory in the case of MRI-detected additional lesions.

If there is a clinically and/or sonographically suspicious axillary lymph node, elastography increases the diagnostic accuracy [28]. Ultrasound-guided fine needle aspiration or core cut biopsy is recommended to avoid 2-stage axillary surgery [29] (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 expression (> 1 – $< 10\%$) were initially regarded as hormone receptor-negative; however, today they are classified as hormone receptor-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 [30–34] 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.

Lesions of Uncertain Malignant Potential (B3)

Among the lesions of uncertain malignant potential that are grouped into the B3 category [35], 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 per-

centage 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 base to guide the management of lesions with uncertain malignant potential has grown, and this has led to a generally more conservative approach. However, the published literature mostly consists of single-institution, non-randomized, retrospective case series, often lacking in careful pathologic-radiologic correlation and concern for possible selection bias for open biopsy. This may explain the variations in the published risks for upgrade to invasive or noninvasive cancer on open biopsy. Taking this into account, the upgrade risk for ADH is estimated at 20–30% compared to 0–10% for the other lesions in question (FEA, LIN, papilloma, radial scar) [36].

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 a recent study, 82% of the open biopsies upgraded after the diagnosis of ADH contained DCIS [37].

FEA is mostly a clinically occult lesion detected through microcalcifications on screening mammography. Several recent studies that included radiological-pathological correlations show low upgrade risks below 10% [38–40]. Therefore, treatment decisions among these patients may be individualized with open biopsy not being necessary in the case of a small lesion (≤ 2 terminal ductal-lobular units in vacuum 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 [41].

Papillomas most frequently present as solitary or multiple central papillomas. They 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 consultation and excision due to a much higher risk for underestimation of cancer [42]. In the case of solitary papillomas, the upgrade risk is much smaller, and, provided that biopsy has been sufficiently representative (6–7 cores, corresponding to 100 mm²) and no discordance to imaging results is evident, conservative management is usually justified [43, 44].

With LIN it must be considered that in the early literature on the risk associated with a diagnosis of LIN, incidental cases of LIN (which are commonly associated with occult microcalcifications) were often not clearly separated from those cases with other radiological abnormalities. Consequently, upgrade rates for LIN are commonly reported to exceed 20% [45]. More recent studies with careful radiological-pathological correlation have reported much lower up-

grade rates for occult lesions with LIN on core biopsy ($< 10\%$) [46–48]. 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 [49]. fLCIS is another form of lobular intraepithelial neoplasia with high risk, and may not infrequently be associated with microinvasion [50, 51]. In the LIN grading system (LIN 1–3), pLCIS and fLCIS are categorized as the most severe grade (LIN 3) [52].

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 radiological-pathological correlation have indicated that open biopsy is not necessary in the case of small lesions and complete removal of the imaging abnormality [53–55].

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 radiological-pathological 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 [56].

Ductal Carcinoma in Situ

DCIS has so far been considered as a local pre-invasive disease that by itself is not life-threatening. The presumption that DCIS is a precursor of invasive cancer led to the recommendation of rigorous local treatment including wide local excision followed by radiotherapy as the standard procedure, or mastectomy in the case of extensive DCIS.

The current treatment strategies have been challenged by the recently published mortality analysis of the Surveillance, Epidemiology and End Results (SEER) registries based on the data of 108,196 women treated for DCIS between 1988 and 2011 [57]. Patients with a diagnosis of DCIS had an overall breast cancer-specific mortality rate of 1.1% and a 1.8-fold higher risk of dying from breast cancer at 20 years (3.3%; 95% confidence interval (CI) 2.17–3.01) compared to the general population. Although invasive recurrences were significantly associated with a higher mortality rate (hazard ratio (HR) 18.1; 95% CI 14.0–23.6), a higher extent of local treatment (BCT vs. mastectomy, radiotherapy vs. nil) did not diminish breast cancer mortality at 10 years, even in an analysis adjusted for age, tumor size, grade, ethnicity, and ER status. These data fuel a growing concern about overtreatment of DCIS, especially if it is detected at mammography screening.

A Cochrane review showed a significant reduction in local recurrence rates by 51% for invasive or noninvasive disease in the ipsilateral breast with the addition of radiotherapy following BCT [58]. However, recurrence rates have been constantly declining in recent years [59]. This translates into a reduced absolute benefit for the individual patient and an increased number of patients to treat. Although, so far, no evidence-based criteria are available to select pa-

tients in whom the recurrence rate is not reduced by radiotherapy, the current rate of 96% of patients being treated with radiotherapy after BCT in Germany appears extremely high in view of the small benefit of some patient groups and the lack of impact on OS.

According to a Cochrane review, postoperative treatment with tamoxifen significantly reduces the rate of ipsi- and contralateral DCIS as well as contralateral invasive disease [60]. There was, however, no significant impact on ipsilateral invasive recurrence. The use of tamoxifen was not associated with a survival benefit. Regarding the relatively small and exclusive preventive benefit of antihormonal intervention in patients with endocrine responsive (ER/PR-positive) DCIS, the AGO acknowledges a high level of evidence for the effect of antihormonal treatment. The balance between benefit and harm appears, however, unclear (LoE 1a/A/AGO +/-).

Two RCTs were published recently that compared tamoxifen and AIs for the adjuvant antihormonal treatment of DCIS. The IBIS II DCIS study concluded that there was no efficacy difference between tamoxifen and anastrozole [61]. NSABP-B35 showed a slight advantage of anastrozole compared to tamoxifen [62]. This difference was, however, restricted to postmenopausal patients < 60 years. Patient-reported outcomes with anastrozole versus tamoxifen were reported from the NSABP-B35 trial [63]. AGO recommends that if adjuvant hormonal treatment for DCIS is considered, the specific side effects of the drug outweigh a potential advantage in terms of recurrences (LoE 1/A/AGO +/-) (for both drugs).

Future research is urgently required to tailor the treatment of DCIS according to its biology and risk for local or systemic recurrence. De-escalation of treatment intensity for low-risk lesions seems an important challenge.

Prognostic and Predictive Factors in Early Breast Cancer

Adjuvant chemotherapy reduces breast cancer mortality by one-third in every risk group defined by conventional pathology and immunochemistry [64]. The individual benefit is closely related to the absolute recurrence risk. Especially in low-risk groups like ER-positive or node-negative tumors, one has to weigh the benefit against the acute and long-term morbidity of chemotherapy.

Conventional pathology and immunohistochemistry are subject to high interobserver variability particularly due to methodological reasons. However, a comparison of large series as part of recently conducted trials showed improved assessment quality with high concordance between central and local pathology for hormone receptor status (97%) and grading (68%) [65]. In the ASCO/CAP guidelines, HER2 discordances are reported in only 6% of cases [66].

Modern genomic platforms generate highly reproducible information about tumor biology and carry the potential to add relevant prognostic information to classical clinical and pathological assessment. Therefore, AGO recommends genomic testing (i.e. EndoPredict® (Sividon Diagnostics GmbH, Cologne, Germany), Prosigna® (NanoString Technologies, Seattle, WA, USA) (LoE 2009 I/B/AGO +), or Oncotype DX® (Genomic Health, Redwood City,

CA, USA) (LoE 2009 I/A/AGO +)) for the identification of patient subgroups with a low enough risk of recurrence to justify avoidance of chemotherapy (supplemental fig. 1, www.karger.com/?DOI=446941).

It has to be acknowledged, however, that these tools should only be used in cases where all other criteria are inconclusive for therapeutic decision-making, as in many cases clinical and pathological parameters (such as negative hormone receptor status, high nodal status or others) suffice for sufficient risk-stratification and indication of therapy. Use of these tests should be limited to patients with ER-positive and HER2-negative disease and 0–3 lymph nodes to predict recurrence risk in the next 5 years or even 5–10 years (Prosigna® and EndoPredict®). There is new retrospective evidence from the ATAC trial involving 928 of the more than 9,000 postmenopausal breast cancer patients treated in this trial. In this cohort, the EP and the EPclin score were highly prognostic for distant recurrence in endocrine-treated patients with ER-positive/HER2-negative disease [67]. In the GEICAM 9906 trial, 555 tumors from 1,246 patients randomized to 2 different chemotherapy regimens (fluorouracil/epidoxifen/cyclophosphamide (FEC) with or without paclitaxel) between 1999 and 2002 were analyzed with EndoPredict®. There were no statistically significant survival differences for patients with low or high EP or EPclin score with regard to the chemotherapy arms, but the authors stated that no event (recurrence) was observed in the group of patients with low EPclin score [68].

In 2015, the first piece of prospective evidence from RCTs was available for the low-risk group in the TAILOR-X trial and for the low-/intermediate- and high-risk group in the PlanB trial (both using Oncotype Dx®). In the TAILOR-X trial, a 5-year distant-free relapse rate of 99.3% was reported in patients with a low-risk situation defined as recurrence score (RS) between 0 and 10. These results are based on 1,226 node-negative patients who received no chemotherapy [69]. In PlanB, according to the inclusion criteria, only node-negative high-risk and node-positive (1–3 positive nodes) candidates for chemotherapy were eligible. 348 (15.3%) patients with RS 0–11 were classified as low risk and did not receive any chemotherapy. 3-year DFS in this group was 98%. In the chemotherapy group, 3-year DFS was 98% for the RS 12–25 group and 92% for patients with RS > 25 [70]. Results from other prospective trials are pending.

The prognostic value of circulating tumor cells (CTC) in primary and metastatic breast cancer is the subject of several publications. CTC detection helps to identify patients with increased risk for relapse/progression (LoE 2009 I/A/AGO +/-) [71]. Nevertheless, the use of CTCs to guide treatment decisions is still not recommended outside clinical trials (LoE 2009 I/A/AGO -).

Neoadjuvant Chemotherapy

Survival rates are similar after primary systemic ('preoperative', 'neoadjuvant') chemotherapy (NACT) and adjuvant therapy [72]. Pathological complete response (pCR) defined as ypT0 ypN0 or ypT0/is ypN0 is associated with improved survival.

NACT is the preferred therapeutic option in patients who have a clear indication for adjuvant postoperative chemotherapy (LoE 1/B/AGO +) (supplemental fig. 2, www.karger.com/?DOI=446941) [73].

In particular, in patient subgroups where a pCR is associated with improved survival such as in triple-negative, HER2-positive, and luminal B like (hormone receptor-positive/HER2-negative/grade 3, high KI 67) cancer, NACT (plus targeted therapy) should be the preferred therapeutic approach (AGO ++) [74]. In patients with TNBC (regardless of *BRCA1/2* 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) [75–79]; the addition of carboplatin was not only associated with an increase in pCR in both neoadjuvant trials, but also resulted in a significant improvement in GeparSixto with a DFS of 85.8% (with carboplatin) vs. 76.1% without carboplatin (HR 0.56; $p = 0.0350$). Furthermore, results of the GeparSepto trial suggest particular benefit from using nab-paclitaxel once weekly instead of paclitaxel among patients with TNBC: pCR occurred more frequently in the nab-paclitaxel group (38%) compared to the solvent-based paclitaxel group (29%, odds ratio (OR) 1.53, 95% CI 1.20–1.95; $p = 0.00065$) (LoE 2b/B/AGO +) [80].

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 hormone receptor-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 (LoE2b/B/AGO +) such as 4× vinorelbine/ capecitabine (LoE1b/B/AGO +) may be beneficial [81, 82]. This can be an option in individual cases but cannot be considered as a routine approach.

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 +/-). Novel predictive factors, such as tumor cell infiltration/lymphocyte-predominant breast cancer (LoE 1/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 not yet applicable to the routine clinical setting [83, 84].

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 +/-). Multicentric lesions should be exactly defined (bicentric, tricentric, AGO +/-) as an individual option, considering the scarce data support for such an approach. Similarly, the remaining tumor load after NACT must be weighed up against breast size (LoE 2b/C/AGO +/-) [85].

Postneoadjuvant 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 controlled trials.

Breast Cancer Surgery under Oncological Aspects

The need for axillary lymph node dissection after preoperative chemotherapy has increasingly been put into question. Preoperative systemic therapy (with or without targeted therapy) offers the possibility of reducing the rate of positive axillary lymph nodes and with that the extent of axillary intervention/surgery.

For the first time, AGO allows SLNB in patients with a cN0 status before or after NACT (supplemental fig. 3, www.karger.com/?DOI=446941).

Classe et al. [86] determined the detection rate, the false-negative rate, and the accuracy of sentinel lymph node (SLN) detection after NACT based upon a prospective multicentric study among 195 patients with advanced large operable breast cancer. They reported a detection rate of 94.6% and a false-negative rate of 9.4% among patients with clinically node-negative disease prior to NACT and concluded that their study confirmed the feasibility and reliability of SLNB after NACT.

Furthermore, there is an increasing body of evidence supporting the use of SLNB among patients that convert from a cN+ status to a ycN0 status through NACT. First, the ACOGSOG Z1071 included clinically node-positive patients who received preoperative chemotherapy. Positive lymph nodes were histologically proven before preoperative chemotherapy ($n = 756$). Patients then underwent both SLNB and consecutive axillary dissection. At least 1 sentinel node was identified in 92.7%. The detection rate was increased by the use of a dual sentinel lymph node detection technique (blue dye only 78.6%; radiolabeled colloid only 91.4%, and radiolabeled colloid with blue dye 93.8%) [87]. Furthermore, the SENTINA study showed that among patients converting after NACT from cN+ to ycN0 (Arm C), the detection rate was 80.1% (95% CI 76.6–83.2; $n = 474/592$) and the false-negative rate was 14.2% (95% CI 9.9–19.4; $n = 32/226$). However, in a subgroup analysis regarding the number of excised SLNs, a decreasing false-negative rate could be demonstrated with an increasing number of SLNs excised. In the case of 3 excised SLNs, a false-negative rate of 7.3% was reported [88].

Similarly, data from Boileau et al. [89] confirmed that axillary lymph node dissection may be avoided in as many as 30% of cases that convert from cN1 to ycN0 through NACT. In their analysis, 153 women with node-positive breast cancer underwent SLNB followed by axillary lymph node dissection after preoperative chemotherapy. The false-negative rate was again lower if a dual tracer method was used instead of a single tracer (5.2 vs. 16%) and if 2 or more SLNs were detected instead of 1 (4.9 vs. 18.2%). The size of postneoadjuvant sentinel node metastases did not correlate with the rate of positive non-sentinel nodes (ypN0(i+) 57%, ypN1mi 0.2–2 mm 38%, <ypN1 > 2 mm 56%).

Based upon these data, SLNB may be performed among patients converting from cN+ to ycN0 in selected cases (with use of a dual tracer and detection of at least 3 SLNs; supplemental fig. 3, www.karger.com/?DOI=446941).

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 [90].

If BCT is not feasible, breast reconstruction with silicone-filled 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 the patient and tumor-related issues. In mastectomy, the preservation of the nipple-areola complex may be performed (LoE 2B/B/AGO ++). The best implant reconstruction (IR) results are achieved if no locoregional irradiation is necessary (LoE/A/AGO ++). If radiotherapy is needed, IR prior to radiotherapy should be the preferred choice (LoE 2a/AGO +) as compared to IR following mastectomy and radiotherapy (LoE/B/AGO +/-). Nevertheless, complications like capsular contraction, necrosis, or infections are described to occur in at least 40% of cases. Synthetic meshes or acellular dermal matrices are possible options for muscle fixation in the case of immediate implant reconstruction (LoE 2b/C/AGO +).

If autologous reconstruction is planned (transverse rectus abdominus myocutaneous (TRAM) flap, deep inferior epigastric perforator (DIEP) flap), 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 +) [91, 92].

The use of lipotransfer is an increasingly employed additional tool to refine breast-reconstructive surgery with no data suggesting an increased risk of disease recurrence so far. Lipotransfer can be performed after mastectomy and implant-based reconstruction (LoE 2a/B/AGO +). After BCT, lipotransfer should only be performed on an individual basis and after detailed informed consent, due to the lack of data (LoE 4/D/AGO +/-).

If implant reconstruction is not suitable, the preferred pedicled TRAM (LoE 3b/AGO +) or the free DIEP flap (LoE 3b/AGO +) may be considered. Comparing both techniques on a data basis without prospective trials, the free tissue transfer is a more time- and personnel-consuming microsurgical procedure associated with a higher rate of reoperation, a higher total failure rate, and no increased patient satisfaction in multivariate analyses. Therefore, ipsilateral pedicled TRAM is recommended (LoE 3b/AGO +) [93].

Adjuvant Radiotherapy

Adjuvant radiotherapy is an essential part of the primary treatment in early breast cancer and contributes substantially to improvements in OS. 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 on adjuvant radiotherapy based on an intense consensus discussion. Disagreement on any statement is highlighted. For technical details on radiotherapy, we agreed to refer to the corresponding updated DEGRO practical guidelines 2014 [94, 95].

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 earlier.

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 [96–98] and common practice [99–101]. 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 ≥ 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 [102].

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

In elderly patients, individual counseling after geriatric assessment is recommended. Omission of radiotherapy is an option particularly for patients with a low risk of recurrence, i.e. ≥ 70 years, pT1 pN0 G1–2, HR-positive/HER2-negative, R0 (> 1 mm), if strict adjuvant endocrine treatment (e.g. tamoxifen 5 years) is performed (LoE 1b/A) [103]. Since there is no influence on OS and side effects can be avoided, the AGO experts accept a slight increase in local recurrence and mastectomy as salvage surgery as an option in the case of recurrence (AGO: AGO +). However, the DEGRO experts do not agree and would not recommend this procedure (DEGRO: AGO +/-). Alternatively, AGO and DEGRO agree that in patients > 70 years, intraoperative accelerated partial breast irradiation (APBI) can be delivered as 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 [104]. With regard to patients with 1–3 infiltrated

nodes (pN1), published data were interpreted differently by AGO and DEGRO; while DEGRO would recommend PMRT for any number of positive lymph nodes, AGO would reserve PMRT for high-risk patients only.

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) [105]; 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 [106, 107]. However, for some patients, individual discussion will be required.

New to the 2016 recommendations is a differentiated indication for the irradiation of the lymph node fields. Radiotherapy of the medial supra/infraclavicular and internal mammary chain lymph nodes consistently improved DFS and distant metastasis-free survival in 2 large RCTs [108, 109] and a Danish population-based study [110], resulting in a small but statistically significant OS benefit in the meta-analyses of these trials [111]. The majority of patients in these trials had either lymph 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 (grade '+') in all cases with pN1b-c, pN2c, and pN3b, in the case of pN2a if G2–3 or ER/PR-negative, in the case of pN1a with lateral tumors if premenopausal and G2–3 or ER/PR-negative, and in the case of pN1a with central or medial tumors if G2–3 or ER/PR-negative. For patients who received trastuzumab, radiotherapy of the mammary chain lymph nodes is not recommended. Radiotherapy of the medial supra/infraclavicular lymph nodes is strongly recommended (grade '++') in the case of pN2a or positive nodes in level III, and also advised (grade '+') in the case of pN1a with lateral tumors if premenopausal and G2–3 or ER/PR-negative and in the case of pN1a with central or medial tumors if G2–3 or ER/PR-negative. Radiotherapy of all axillary lymph nodes is recommended (grade '++') if residual tumor is left after dissection, and might be considered (grade '+/-') in the case of 1–2 positive SLNs as an alternative to axillary dissection or no specific axillary therapy.

Adjuvant Endocrine Therapy

Endocrine therapy represents the most important option in the adjuvant treatment of estrogen-responsive early breast cancer. Treatment decisions for this targeted therapy are based on proof of endocrine sensitivity (ES) by well-established predictive factors. ES, by definition, requires a staining positivity for the tumor cells of at least 1% for either ER or PR. For the determination of menopausal status, measurement of estradiol (E2) and follicle-stimulating hormone (FSH) represents the method of choice.

Acknowledging data with regard to the integration of extended adjuvant treatment (EAT) strategies using i) tamoxifen (as shown by the ATLAS 84 and aTTom [112] trials) or ii) AIs (as demon-

strated for instance in the MA.17 trial [113]) the following general recommendations can be given for adjuvant endocrine therapy (AGO ++):

Standard treatment duration 5 years: tamoxifen in premenopausal, tamoxifen or AI in postmenopausal patients;

Treatment up to 10 years may be considered based on individual risk of relapse (e.g. N+ status);

Premenopausal: after 5 years of tamoxifen, EAT (further 5 years of tamoxifen)

Postmenopausal: after 5 years of tamoxifen, EAT (further 5 years of tamoxifen or AI);

Duration, choice, and sequence of AIs or tamoxifen mainly depend on menopausal status, risk of relapse, and side effects;

Switching to another endocrine treatment (tamoxifen or AI) is better than stopping;

AI as first treatment preferably in postmenopausal patients at high risk and or with lobular cancers;

Endocrine treatment should involve AIs in the first 5 years to some extent;

No evidence for AIs > 5 years;

In premenopausal women, administration of tamoxifen for 5–10 years is the standard regimen (LoE 1a/A/AGO ++). Treatment should be performed as long as tolerable and as long as patients stay premenopausal. A switch to an AI when patients become postmenopausal may be considered as well as a prolongation of therapy up to 10 years with tamoxifen.

The TEXT and SOFT trials investigated the effect of ovarian function suppression (OFS) in the context of adjuvant endocrine therapy for women with premenopausal breast cancer. Application of GnRH in combination with tamoxifen or exemestane was compared to tamoxifen monotherapy [114]. While in TEXT all patients were treated with GnRH from the beginning, in SOFT only those patients with premenopausal status 8 month after completion of chemotherapy were allowed to enter the trial. Due to low event rates, a joint analysis of the TEXT and SOFT trials comparing tamoxifen versus OFS + tamoxifen versus OFS + exemestane was performed. Adding OFS to tamoxifen did not provide a significant benefit in the overall study population. However, there was a difference between the OFS + tamoxifen versus OFS + exemestane groups. After a median follow-up of 68 months, DFS at 5 years was 91.1% in the exemestane-OFS group and 87.3% in the tamoxifen-OFS group (HR for disease recurrence, second invasive cancer, or death: 0.72; 95% CI 0.60–0.85; $p < 0.001$). With 194 deaths (4.1% of the patients), OS did not differ significantly between the 2 groups (HR for death in the exemestane-OFS group: 1.14; 95% CI 0.86–1.51; $p = 0.37$) [115]. An additional retrospective exploratory analysis of the SOFT trial indicated that the major effect was seen in younger patients under 35 years of age, who received adjuvant chemotherapy due to higher risks such as high-grade invasive breast cancer and lymph node positivity with an improvement for DFS (67% for the tamoxifen only group vs. 78.9 for OFS + tamoxifen vs. 83.4% for OFS + exemestane). Therefore, the addition of OFS to endocrine treatment may be considered in patients with persistent ovarian function (within 8 months) after adjuvant chem-

otherapy: OFS 5 years + tamoxifen 5 years (LoE 1b/B/AGO +/-) or OFS 5 years + AI 5 years (LoE 1b/B/AGO +/-). However, increased side effects may lead to impaired patient compliance.

For postmenopausal patients, the following treatment options are available:

Years 0–5:

5 years of AI (which may be used preferentially in high-risk populations and lobular cancers);

Sequential therapy for 5 years (AGO ++);

Tamoxifen (2–3 years) followed by AI (up to year 5) (LoE 1a/A);

AI (2–3 years) followed by tamoxifen (up to year 5) (LoE 1b/C).

Years 5–10:

After 5 years of tamoxifen: an additional 5 years of tamoxifen or AI;

After 5 years of AI: no further endocrine therapy recommended;

After 5 years of sequential therapy: no further endocrine therapy recommended.

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 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 either in DFS or in OS after a median follow-up period of 82.8 months ($p = 0.74$ and 0.65 , respectively) [116]. An analysis of hormone receptor 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 ; supplemental fig. 4, www.karger.com/?DOI=446941).

Standard adjuvant chemotherapy consists of combination regimens based on anthracyclines and taxanes in patients with a HER2-negative tumor (LoE 1a/A/AGO ++). Treatments of choice include $4 \times$ EC/AC, followed by $12 \times$ paclitaxel (every 7 days, q7d), or $4 \times$ docetaxel (q21d), or treatment with $6 \times$ DAC (AGO ++). These combination regimens have recently been confirmed using the 10-year data from E1199 [117]. Here, regimens with docetaxel 3-weekly (100 mg/m^2 body surface area (BSA) q21d), docetaxel weekly (35 mg/m^2 BSA q7d), paclitaxel 3-weekly (175 mg/m^2 BSA q21d), or weekly paclitaxel (80 mg/m^2 BSA 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 ben-

efit 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 represents an alternative (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 [118, 119].

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 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 duration is 1 year (LoE 1b/A/AGO ++ [120]). 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 +/- [121]). 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 $< 3 \text{ cm}$ and negative nodal status, treatment with $12 \times$ paclitaxel q7d (LoE 2b^a/B/AGO +/- [122]). With regard to alternative anti-HER2 treatments, neither lapatinib nor dual therapy with lapatinib plus trastuzumab can currently be recommended (LoE 1b^a/B/AGO -). The results of the ALTT0 study showed no advantage with regard to DFS or OS either for sequential trastuzumab and lapatinib or for the combination [123]. However, in the subgroup of hormone receptor-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 [124] (LoE 1b/A/AGO -/-), while topical vaginal application of estriol may be used for urogenital symptoms [125] (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% [126]).

The majority of studies regarding 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 [127]. Increased pharmacovigilance for herbal medicines is required, e.g. initiatives to stimulate reporting of suspected adverse reactions. Neither flax seed [128] nor black cohosh (*Cimicifuga racemosa*) [129] nor St. John's wort [130] nor ginseng root [131] could improve menopausal symptoms.

Five RCTs 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 taking tamoxifen does not indicate 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 [132].

A systematic review and meta-analysis of 11 RCTs showed that red clover had a positive effect on alleviating hot flushes in menopausal women (LoE 1b/B/AGO +/-). Slight changes were found in 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 [133].

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 +) [134].

Mind-body medicine (MBM; relaxation training, yoga, hypnosis) is reported to result in a moderate and even significant improvement in hot flushes score, joint pain, fatigue, sleep, mood, and relaxation (LoE 1b/B/AGO +/+) [135, 136]. 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 [137] (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 +/-) [138].

Contraception

All patients of childbearing potential must be counseled about adequate contraception during systemic therapy [139], since cytotoxic 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 +) [140]. 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

This year, we focused on updating LoEs and GRs of existing slides in this chapter due to a lack of sufficient new data. As before, 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.

Use of ginseng following the diagnosis of breast cancer has not been demonstrated to improve the quality of life of breast cancer survivors. Use of *ganoderma lucidum* (an oriental fungus) was associated with better social wellbeing but poorer physical wellbeing scores [141]. Similarly, available data suggests that oral administration of curcumin (6.0 g daily) during radiotherapy may result in a reduction in the severity of radiation dermatitis in breast cancer patients [142].

Acknowledging patients' needs to contribute to the treatment of their breast cancer, cessation of cigarette smoking has been emphasized more strongly compared to previous years [143]. 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 and disease-specific as well as general health effects are linked by a reduction in obesity which has clearly been demonstrated to improve OS and DFS [144]. More specifically, newer data suggests that high-fat dairy products should be avoided [145]. Notably, this year, we alleviated our recommendations with regard to some complementary treatments for recurrence prevention that we previously suggested to strictly avoid. Scientific evidence suggests that i) vitamin and/or antioxidant supplements do not jeopardize disease outcome, and ii) particularly vitamins C, E, and D might have some beneficial effects [146–148]. In contrast, artificial carotenoids should be viewed with caution [149]. There is no reliable data showing that patients should sustain from adding moderate amounts of soy products to their diet; however, daily intake of soy concentrates containing > 100 mg of isoflavonoids will have to be tested for safety before it can be recommended [150]. Current evidence does not support an association between intake of black cohosh and increased risk of breast cancer [151]. For acupuncture, evidence of benefit was found concerning cancer treatment-related nausea and vomiting. Benefit was also reported for other cancer-related symptoms, including pain, fatigue, hot flushes, xerostomia, dyspnea, and anxiety. Reviewers found a paucity of rigorous trials and heterogeneity of populations, interventions, controls, and outcome measures, which challenges the process of systematic review and meta-analysis.

Acupuncture should be considered for symptom management given the lack of sufficient treatment options [152]. Mindfulness-based stress reduction is an 8-week program aiming at developing participants' coping resources and mindful awareness. The pro-

gram consists of guided meditation, guided body scan (a specific awareness exercise) and meditation, and yoga. Psychoeducation tackles stress and stress reactions. Reviews and meta-analyses in breast cancer patients showed positive effects on mental health status. A meta-analysis by Cramer et al. [153] including only RCTs reported mild effects on depression and moderate effects on anxiety.

Online Supplemental Material

Supplemental Fig. 1. Recommendations regarding prognostic factors

Supplemental Fig. 2. Subtype-specific general systemic strategies

Supplemental Fig. 3. Recommendation regarding axillary staging before or after neoadjuvant chemotherapy (NACT)

Supplemental Fig. 4. Adjuvant chemotherapy without concurrent trastuzumab

To access the supplemental material please refer to www.karger.com/DOI/446941.

Disclosure Statement

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References

References can be found in the appendix; please refer to www.karger.com/DOI/446941.