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AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2022

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Keywords

Early breast cancer · Postneoadjuvant therapy · Breast surgery · Reconstruction · Radiotherapy · Communication

Abstract

Introduction: The AGO (Arbeitsgemeinschaft Gynäkologische Onkologie, German Gynecological Oncology Group) Task Force on Diagnosis and Treatment of Breast Cancer as an interdisciplinary team consists of specialists from gynecological oncology, pathology, diagnostic radiology, medical oncology, and radiation oncology with a special focus on breast cancer. ***Methods:*** The updated evidence-based treatment recommendation 2022 for early breast cancer (EBC) and metastatic breast cancer of the AGO Task Force has been released. ***Results and Conclusion:*** This paper captures the update of EBC.

Introduction

Breast cancer is the most frequent cancer in the European Union, encountering >400,000 new cases per year and thus, the most frequent cancer in women. For women diagnosed with early breast cancer (EBC), the 5-year survival probability is about 96% in Europe. A multidisciplinary team is a prerequisite for optimal management of breast cancer. The AGO (Arbeitsgemeinschaft Gynäkologische Onkologie, German Gynecological Oncology Group) Task Force on Diagnosis and Treatment of Breast Cancer as an interdisciplinary team consists of specialists from gynecological oncology, pathology, diagnostic radiology, medical oncology, and radiation oncology with a special focus on breast cancer.

The updated evidence-based treatment recommendation 2022 for EBC and metastatic breast cancer (MBC) of the AGO Task Force has been released. This paper captures the update of EBC while the topics of MBC will be updated by Thill et al. The full version of the updated slide set including annotated speeches of each chapter is available online (www.ago-online.de/ago-kommissionen/kommission-mamma) in English and German [1]. In addition, there is a version for patients from this live event available. This update has been performed according to a documented algorithm, by thoroughly reviewing and scoring chapter by chapter the most recent and relevant publications for their scientific validity (Oxford level of evidence (LoE) [2] and clinical relevance (AGO grades of recommendation; Table 1–3).

Options for Primary Prevention and Lifestyle Factors

Primary prevention is defined as preventing disease or injury before it ever occurs. This is done by preventing exposure to hazards that cause specific diseases.

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

Relevant lifestyle factors such as overweight/obesity, physical inactivity, fiber-containing foods, alcohol consumption (LoE2a/B), smoking (LoE2a/B), and exposition to ionizing radiation are well known. Adherence to normal body weight (BMI 18.5–25 kg/m^2) as a preventive factor for the development of breast cancer is well investigated, particularly for postmenopausal women (LoE 2a/B/++). For bariatric surgery, there is increasing evidence for a reduction in breast cancer risk [3]. A balanced diet including extra virgin olive oil (LoE2b/B/AGO+), nuts (LoE 2b/B/AGO+) (>10 g/die), reduced consumption of fat (LoE2a/B/AGO+), and reduced consumption of red meat (LoE2b/C/AGO+) may decrease the incidence of breast cancer. For other factors such as supplementation of vitamin D3 (LoE1b/B/AGO+/−), vegetarian or vegan diet (LoE2b/C/AGO+/−), vegetables and fruits (LoE2a/B/AGO+/−), dairy products or phytoestrogens (LoE2a/B/AGO+/−), the data are contradictory regarding the reduction of breast cancer incidence [4, 5]. However, it should be considered that prospective randomized trials to investigate the impact of nutrition aspects on breast cancer risk are almost impossible to conduct. In

Table 1. Oxford Levels of Evidence (LOE)

LOE	Therapy/prevention, aetiology/harm	Prognosis
1a	Systematic review (with homogeneity) of randomised controlled trials	Systematic review (with homogeneity) of inception cohort studies; clinical decision rule validated in different populations
1b	Individual randomised controlled trials (with narrow confidence interval)	Individual inception cohort study with ≥80% follow-up; clinical decision rule validated in a single population
1c	All or none	All or none case-series
2a	Systematic review (with homogeneity) of cohort studies	Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomised controlled trials
2b	Individual cohort study (including low quality randomised controlled trials; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in a randomised controlled trials; derivation of clinical decision rule or validated on split-sample only
2c	"Outcomes" research; ecological studies	"Outcomes" research
3a	Systematic review (with homogeneity) of case-control studies	
3b	Individual case-control study	
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology. Bench research or "first principles"

Table 2. Oxford GR

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies **or extrapolations from level 1 studies**
C	Level 4 studies **or extrapolations from level 2 or 3 studies**
D	Level 5 evidence **or troublingly inconsistent or inconclusive studies of any level**

GR, grades of recommendation.

Table 3. AGO grades of recommendation

++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restrictions, 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

contrast, physical exercise (metabolic equivalents to 3–5 h moderate pace walking per week) has been demonstrated to be efficient in reducing breast cancer risk (LoE2a/B/AGO++). Pregnancy related factors (number of full-term pregnancies (LoE2b/B), first delivery before the age of 30 years (LoE2b/B), duration of breast feeding (LoE3a/B) may be preventive for breast cancer, whereas PCO syndrome (LoE3b/C), assisted reproduction (LoE2b/B), and abortion (LoE2b/B) do not influence the risk for EBC [6].

Avoidance of hormone replacement therapy (especially estrogen/progestin combination regimens) in postmenopausal women may reduce breast cancer risk (LoE1b/A/AGO+). Oral contraceptives do not increase the probability of death from breast cancer (LoE1a).

Regarding chemopreventive agents other than endocrine therapy, the effects of 5-Aminosalicylsäure, bisphosphonates [7], and statins have been evaluated. Some encouraging results suggest that 5-Aminosalicylsäure use might reduce breast cancer risk, particularly regarding hormone receptor positive or in situ breast tumors and postmenopausal women (LoE4D/D/+/–). Bisphosphonates are rated (LoE2b/B/AGO+/–) for primary prevention of breast cancer.

Breast Cancer Risk, Genetics, and Prevention

The AGO Mamma still recommends genetic counseling and testing based on individual and family history (LoE2b/B/AGO++) [8]. The evidence for the risk assess-

Table 4. Breast cancer risk and minor allele frequency [9]

	Near population risk of breast cancer, %	Moderate risk of breast cancer, %	High risk of breast cancer, %
Lifetime risk from age 20	Less than 17	Greater than 17 but less than 30	30 or greater
Risk between ages 40 and 50	Less than 3	3–8	Greater than 8

ment of different gene mutations is steadily increasing. According to the data solidified in recent years, the following assessment applies (Table 4).

Pathogenic mutations with a proven clinical benefit of a genetic test are BRCA1/BRCA2 (LoE1b/A/AGO++), PALB2 (LoE3a/B/AGO+), CDH, PTEN, TP53, STK11 (LoE3b/B/AGO+), and ATM, BARD1, CHEK, RAD51C/D (LoE3a/B/AGO+/−) with varying degrees of evidence. New in the context of risk calculation is an increasing individualization through the inclusion of the polygenic risk score (PRS) and nongenetic risk factors. In addition, there are new treatment options for BRCA1 and BRCA2 mutation carriers. The recently released striking evidence of the PARP inhibitor olaparib in breast cancer patients with BRCA1/2 germline mutations (gBRCA1/2mut) on IDFS and OS after neoadjuvant or adjuvant therapy in Her2 negative EBC results in a recommendation for olaparib in patients with gBRCA1/2 mutation in EBC (LoE1b/B/AGO+). Thus, genetic testing should be offered according to the currently existing inclusion criteria of this trial [10, 11].

New evidence with gene mutation analysis in more than 113,000 women proved that mutations in BRCA1/2 and PALB2 are associated with a lifetime risk of breast cancer risk of approximately 40%, while ATM, BARD1, CHEK2, RAD51C, and RAD51D are associated with lifetime risk of about 20–30% [12]. The breast and ovarian risk range for PALB2 underlies the need to move away from compartmentalizing PALB2 and consider risk to be a continuous variable from high to moderate, influenced by family history, PRS, and other factors. The same applies to other breast cancer genes [13].

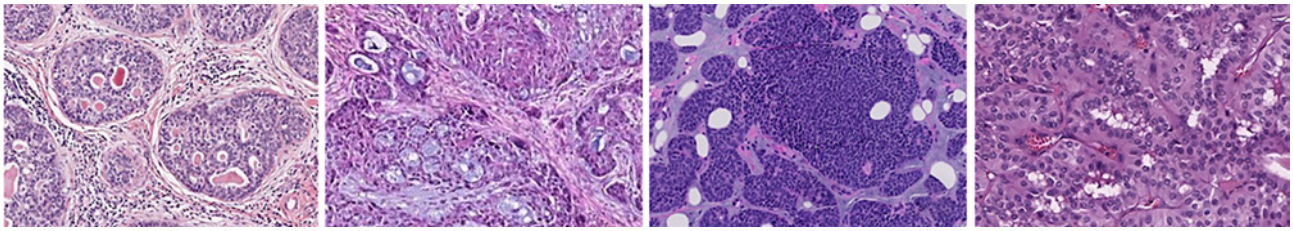
Taking PRSs into account, more than 95% of BRCA1, BRCA2, and PALB2 carriers had >20% lifetime risks of BC, whereas, respectively, 52.5% and 69.7% of ATM and CHEK2 carriers without first-degree relatives with BC, and 78.8% and 89.9% of those with a first-degree relative with BC had >20% risk. PRS facilitates personalization of BC risk among carriers of pathogenic variants in predisposition genes. Incorporating PRS into BC risk estimation may help identify >30% of CHEK2 and nearly half of ATM carriers below the 20% lifetime risk threshold. Changing this paradigm will allow us to move to personalized risk estimates in the context of other risk factors and develop strategies to translate this information to enhance individualized medical management [13, 14]. To test the efficacy of preventive and therapeutic strategies based on this risk calculation, participation in prospective studies or in registers is recommended.

Breast Cancer Diagnostics

In asymptomatic women, biannual mammography (MG) screening is highly recommended for women 50–69 years of age (LoE1a/A/AGO++). In the age of 40–44 years, MG-screening is not recommended (LoE1b/B/AGO−); from 45 to 49 and 70 to 74 years, individual shared decision-making is recommended and a clear indication is necessary (LoE1a/B/AGO+). In women ≥75 years of age, screening can be offered to women in good health with a life expectancy of 10 years or longer (LoE4/C/AGO+/−) [15].

Breast density is a known risk factor for breast cancer development and decreased MG sensitivity. Nevertheless, neither the use of hand-held breast ultrasound (US) nor automated whole breast US can be recommended as a sole modality for screening (LoE3a/C/AGO−) [13]. Using digital breast tomosynthesis, the recall and biopsy rates were low (LoE1a/B/AGO+) [16]. Synthetic 2D image reconstruction of the 3D dataset can significantly reduce radiation dose and is highly recommended (LoE1a/B/AGO++) [17, 18]. Nevertheless, it is very important to use the complete dataset for diagnosis and provide it for the subsequent treatment [16]. In a recent randomized controlled trial, magnetic resonance imaging (MRI) in the extremely dense breast screening group with negative MG showed a significantly reduced interval cancer rate at the cost of slightly increased false-positive cases (LoE1b/B/AGO+) [19, 20].

For patients with symptoms, clinical breast examination (LoE3b/B/AGO++), MG (LoE1b/A/AGO++), digital breast tomosynthesis (LoE2a/B/AGO+) or contrast-enhanced MG (LoE2a/B/AGO+), US (LoE2b/B/AGO++), and minimally invasive biopsies (LoE1c/A/AGO++) should be performed [21, 22]. US of the breast (LoE2b/B/



a
Adenoid-cystic carcinoma

b
Secretory carcinoma
ETV6-NTRK3 gene fusions

c
Polymorphous carcinoma
PRKD1 E710D
PRKD1 / PRKOZ / PRKD3 rearrangements

d
Tall cell carcinoma with reversed polarity
IDH2 hotspot mutations

Fig. 1. a–d Rare and salivary-type TNBC: tumors with divergent clinical behavior and specific genetic alterations.

AGO++) and the axilla is recommended (LoE2a/B/AGO++) as a preoperative routine diagnostic method prior to breast surgery [23, 24]. MRI can be helpful in patients with a reduced sensitivity of MG and US, nipple involvement, lobular invasive cancer, suspicion of multilocular disease, and/or high risk (LoE1b/B/AGO+), provided that MRI-guided vacuum-assisted biopsy access is available in-house or among cooperating partners [19]. Second-look US is recommended in cases of newly detected lesions by MRI. In patients with clinically and/or sonographically suspicious axillary lymph nodes, core needle biopsy is recommended (LoE2b/B/AGO++). If biopsy reveals lymph node involvement prior to neoadjuvant chemotherapy (NACT), a clip should be inserted in the lymph node after biopsy to allow targeted axillary dissection (TAD) at the time of surgery.

Staging is recommended for candidates scheduled for (neo)adjuvant chemotherapy including CT (chest/abdomen) and bone scans (LoE2b/B/AGO+). PET-CT should be reserved for individual cases with high-stage (III) cancer (LoE2b/B/AGO+/–) [25].

Pathology

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

Besides the routinely indicated pathological evaluation of the tumor (histologic tumor type (LoE3b/C/AGO++) taken by core needle biopsy, particular attention is paid to the immunohistochemical determination (estrogen and progesterone receptor [LoE1a/A/AGO++], Her2 new [LoE1a/A/AGO++], reporting of Ki67 positive nuclei as percentage [LoE5/D/AGO++], grading [LoE5/D/AGO++]). Therapy decisions are based on that information, partially including further diagnostics like gene expression profiles.

In the case of clearly triple-negative EBC (TNBC), there are clear therapeutic procedures. But the recommendations become more difficult if ER or PR are only low-positive. Therefore, the use of diagnostic terms in histopathology must be carefully weighted in the light of clinical decision-making. It has become evident that invasive breast cancer of no special type having low hormone-receptor (HR) and negative HER2 status shows a similar response to NACT and adjuvant chemotherapy as TNBC. Therefore, patients with low HR expression are candidates for therapy strategies targeting TNBC [26], and a 10% cutoff of ER expression has been recommended [27]. Clearly, this should be restricted to breast cancers of no specific type sharing other characteristics of TNBC, such as high Ki-67.

Also, in this edition of the AGO recommendations, we have outlined three rare categories of TNBC with specific tumor biology, clinical behavior, and treatment response. This includes apocrine TNBC, metaplastic TNBC, and TNBC characterized by specific molecular alterations.

Apocrine TNBC is characterized by a luminal phenotype (no basal markers), high expression of the androgen receptor, and low tumor proliferation. Clinically, patients with apocrine TNBC are older, have smaller tumors, and have a better survival, compared to nonapocrine TNBC [28, 29]. These patients may be subject to de-escalation in systemic therapy [30]. TNBC with specific molecular alterations include adenoid-cystic carcinoma [31, 32], secretory carcinoma [33], polymorphous carcinoma [34] or the tall cell carcinoma with reversed polarity (see Fig. 1) [35]. Generally, these rare types of TNBC are characterized by a more favorable outcome, compared to TNBC of no special type. Within this year, the predictive PDL1 assay CPS (combined positive score) is rated the same as the IC (Immune Score) based on the new valid data of the Keynote studies, which are presented in more detail in the chapter of adjuvant chemotherapy.

Lesions of Uncertain Malignant Potential (B3)

Lesions of uncertain malignant potential (B3) are usually detected by MG or US and diagnosed by core or vacuum-assisted biopsy (VAB) in asymptomatic women. The risk of developing invasive cancer associated with B3 lesions can be categorized according to the type of lesion (atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), LIN, papilloma, radial scar (RS)), in addition to clinical and pathological factors. The indication for complete surgical excision of B3 lesions is to exclude any upstaging of more severe precursor lesions (ductal carcinoma in situ (DCIS)) or invasive lesions.

ADH has a particularly high risk of being associated with breast cancer when combined with BIRADS IV/V and high breast tissue volume. In fact, ADH on core biopsy may represent inadequately sampled DCIS. Therefore, it has to be treated with an open excision after histopathologically confirmation in core-/vacuum needle biopsy (LoE3a/C/AGO++).

In cases of biopsy of classical LIN, open excision can be avoided if no discordant imaging, especially no focal lesion, is present (LoE2b/C/++) [36]. In contrast, high-risk variants of lobular neoplasia, which include pleomorphic and florid LCIS, are recommended for open biopsy, and preferably complete excision (LoE2b/C/AGO++).

FEA is upgraded to DCIS or invasive breast cancer in 5% of all cases. Open biopsy is recommended (LoE2b/B/AGO+) if vacuum biopsy cannot remove ≥90% of the lesion [37].

The diagnosis of solitary or multiple papillomas on core biopsy might be associated with an increased risk of 30% (with atypia) for an invasive carcinoma or DCIS [38]. Therefore, in case of an atypia or multiple lesions, an open biopsy is mandatory (LoE3a/C/++).

A RS may mimic carcinoma mammographically because of its stellate appearance. Radial sclerosing lesions are only rarely associated with atypia or DCIS. When RS is associated with atypia (such as FEA, ADH, or classical LIN), management can be similar to atypia alone [39]. Medical prevention (e.g., low-dose TAM (TAM) (LoE2b/B/AGO+/−) or aromatase inhibitor AIAIs (AI) (LoE 1b/A/AGO+/−) for lesions with uncertain biological behavior may be performed only in very individual cases [40].

Prognostic and Predictive Factors

Locoregional tumor burden together with tumor biology are the known major prognostic drivers and the key determinants of therapy decisions in EBC. Multigene Assays are well established in node negative disease, HR positive and HER2 negative disease and might help guiding treatment decisions in situations where clinical prognostic factors, such as ER status, grading and Ki67, are not conclusive to decide on endocrine adjuvant therapy or the indication for chemo-endocrine therapy. Age, pCR, and obesity continue to be prognostically relevant factors in EBC. New is the significant association of pCR (pathological complete response) probability and overweight investigated in a meta-analysis [41]. It was demonstrated that overweight/obese women were less likely to achieve pCR after NACT as compared to under-/normal weight women (odds ratio [OR] = 0.80; 95% confidence interval [CI]: 0.68–0.93). Eleven studies provided data of three BMI groups (BMI < 25, 25 ≤ BMI <30, and BMI ≥ 30). Based on pooled analyses, both overweight and obese groups were less likely to achieve pCR with NACT as compared to the under-/normal weight group (OR = 0.77, 95% CI: 0.65–0.93 and OR = 0.68, 95% CI: 0.61–0.77, respectively). Thus, obesity is a negative predictive factor for achieving a pCR after neoadjuvant therapy (LoE2a/B/AGO+). At present, in patients with an increased risk of recurrence in Her2-negative disease, genetic counseling and testing for BRCA1/2 mutations should be a standard procedure to allow the use of olaparib for 1 year as mentioned above (chapter Breast Cancer Risk, Genetics, and Prevention).

In HR-positive/HER2-negative EBC presenting with a Ki67 > 20% derived from the core needle biopsy a short-term endocrine therapy using TAM or AI for 2 weeks might allow to monitor a dynamic Ki67 change evaluated on the surgical specimen. A drop in Ki67 level might indicate endocrine sensitivity and might help to avoid adjuvant chemotherapy in endocrine sensitive EBC. In any case, avoidance of using multigene assays after neoadjuvant endocrine therapy is recommended.

Table 5. DCIS, upstaging, ipsi-/contralateral events and mortality [42, 43]

Upstaging to BC	Ipsilateral events (cum. incidence), %	Contralateral events (cum. incidence), %	BC-specific mortality, % (95% CI)
5–25.9%	*10 years* BCS: 24.6 BCS and radiotherapy: 9.6 *20 years* BCS: 30.6 BCS and radiotherapy: 18.2	*10 years:* 4.8–6.4 *15 years*: 6.4–~11	*10 years* 0.9 (0.7–1.1) (BCS) 0.8 (0.7–1.0) (BCS and radiotherapy) 1.3 (1.1–1.5) (unilateral mastectomy)

Ductal Carcinoma in situ

DCIS is a preinvasive lesion that is considered to be a precursor to invasive breast cancer. Nevertheless, not all DCIS will progress to invasion. Exact figures on upstaging, ipsi- and contralateral disease, and mortality are presented in Table 5.

In addition to MG, which is the main diagnostic tool, pretherapeutic assessment in DCIS should also include breast US, especially to rule out an accompanying invasive component and solid parts (LoE4/C/AGO++) [44]. Breast MRIs may be helpful for assessment of the extension and planning surgical procedure in DCIS (LoE1a/B/AGO+/–), but they can lead to over- and underestimations of the extension of the DCIS as it represents an extremely heterogeneous group of lesions with variable potential for progression to invasive disease [45]. Complete surgical excision remains the standard of care (LoE1a/A/AGO++). Almost all guidelines recommend clear margins of 2 mm for pure DCIS. SNLB might be recommended in rare cases if the surgical procedure is not allowing a SLN in case of an upstaging to invasive cancer (e.g., cases of mastectomy, LoE3b/B/AGO+). Radiotherapy is recommended after BCS of DCIS (LoE1a/A/AGO++). Regarding systemic treatment, patients should be informed that adjuvant endocrine treatment has no impact on survival (LoE1a), but may have a small effect on ipsilateral invasive and DCIS recurrences and on contralateral invasive and noninvasive cancers (LoE1a).

Within this year, Oncotype DX DCIS Score [46] and DCISionRT [47] are newly included as prognostic factors for an ipsilateral recurrence after first diagnosis of a DCIS (LoE2b). The Oncotype DCIS Score is a multigene assay that has been independently validated in a prospective clinical trial and a population-based cohort. The score helps to identify a subset of women >50 years old with unifocal disease that carries <10% risk of any local recurrence after breast-conserving surgery alone. DCISionRT provided information that significantly changed the recommendations to add or omit RT. Compared with traditional clinicopathologic features used to determine recommendations for or against radiotherapy (RT), the factor most strongly associated with RT recommendations was the DCISionRT result, with other factors of importance being patient preference, tumor size, and grade [47].

Breast Cancer Surgery under Oncological Aspects

Surgery is part of the multidisciplinary therapeutic approach in EBC. A delay of ≥4 weeks in cancer treatment should be avoided (AGO+). Survival rates after BCS followed by radiation therapy are at least equivalent to those after mastectomy (LoE1a/A). In nonpalpable BC, wireless intraoperative US localization is associated with a significantly higher negative margin rate compared to wire-guided localization (LoE1a/A/AGO++) [48]. Importantly, the lesion must be visualized by US by the same examiner pre- and intraoperatively. For this procedure, adequate equipment and training of the surgeon are mandatory. "No ink on tumor" remains the accepted standard for clear margins for all patients with invasive cancer, with or without an extensive in situ component (LoE2a/A/AGO++).

Sentinel lymph node excision (SLNE) is the standard of care staging procedure in patients with invasive disease and cN0 (LoE1b/A/AGO++). Axillary intervention can be omitted in patients ≥70 years of age or with severe comorbidity, pT1, cN0, HR positive, HER2 negative, and with an indication for endocrine treatment alone (LoE3b/B/AGO+/–). In patients planned for NACT, clinically (palpation/US) unsuspicious lymph nodes require no pre-NACT surgery or core needle biopsy. After NACT and ycN0, a SLNE is recommended (LoE2b/B/AGO++). Depending on ypN(sn) status, axillary lymph node dissection (ALND) is recommended with different grades: ypN0 (i+) (sn) AGO+/–, ypN1mi (sn) AGO+, ypN1 (sn) AGO++. Suspicious lymph nodes should be evaluated before NACT by core needle biopsy and marker placement. For patients who presented initially with (CNB proven) positive axillary lymph nodes (pN+) and converted to ycN0 after NACT, the accuracy of SLNE (LoE2b/B/AGO+/–) is lower than in the adjuvant setting.

However, if 3 or more negative SLNs alone were removed and nodal radiotherapy was performed, the local recurrence rate is very low [49]. Since unselected axillary sampling is not indicated and ALND (LoE2b/B/AGO+) may be harmful, TAD (LoE2b/B/AGO+) offers an alternative in these patients. However, in case of extensive axillary tumor load (≥4 suspicious nodes) at presentation TAD (SLNE target lymph node(s) extirpation) should be used with caution (LoE5/D/AGO+/−). Caudle et al. [50] described a significant reduction of FNR from 10.1% with SLNE alone to 4.2% with TLNE alone, and 1.4% in case of a combination of SLNE and TLNE (TAD). The impact of different TAD staging procedures on disease-free survival and quality of life is lacking. In case of residual tumor burden (ypN1mi; ypN+) after TAD, ALND is recommended (LoE2b/B/AGO+); in case of residual isolated tumor cells only (ypN0[i+]), therapeutic consequence is still unclear and has to be specified in accordance with the results of ongoing studies (LoE2b/B/AGO+/−; e.g., AXSANA trial) [51].

Oncoplastic and Reconstructive Surgery

Oncoplastic surgery is an essential component in the treatment strategy for breast cancer patients [52]. It is defined as the use of simultaneous reconstructive techniques during breast cancer surgery offering an optimal outcome optimizing quality of life without any compromises towards oncological safety. Compared to 2021, we identified no practice-changing findings.

Oncoplastic surgery focuses on optimized scar positioning, adequate soft tissue shaping, the choice of a suitable reconstruction procedure, and reconstruction of the contralateral breast in order to achieve symmetry. Valid evidence is lacking for the majority of important questions. For implant-based reconstruction, pre- and subpectoral implant placement with or without additional devices (either synthetic or autologous like acellular dermal matrices) can be performed. Participation in studies to evaluate these procedures should be supported [53]. Perioperative systemic antibiotic prophylaxis for implant-based reconstruction is recommended to be performed no longer than 24 h (LoE 2a/B/AGO+), and topical antibiotics/antiseptics should be used frequently as surgical site infection can be decreased significantly when compared to no topical antibiotics (LoE2a/B/AGO+); moreover, it reduces the rate of capsular contraction [54]. Regarding prevention of capsular contraction, there is good evidence for textured implants (LoE1a/A/AGO+) and the use of acellular dermal matrices (LoE2a/B/AGO+) [55] and synthetic meshes (LoE3a/C/AGO+) when compared to nothing. Povidone-iodine has become an option again (LoE2a/B/AGO+/−). Use of leukotriene antagonists (LoE2a/B/AGO−) still has limited data regarding their long-term toxicity; no benefit is seen when breast massage is performed (LoE3a/C/AGO−). In cases of the presence of capsular contraction, capsulectomy and capsulotomy have old but consistent data (LoE3b/C/AGO+). If using textured implants or performing capsulectomy/capsulotomy, one has to be aware of breast implant-associated anaplastic large-cell lymphoma BIA-ALCL (see also chapter special situations with included recommendations). Last is a recently recognized non-Hodgkin's lymphoma of T-cell origin. Despite the low incidence of this new disease, the increasing use of breast implants for cosmetic or postmastectomy reconstruction purposes places BIA-ALCL as an emerging and compelling medical challenge. The real BIA-ALCL pathogenesis has not been fully uncovered so far. Breast implants with textured surfaces seem to be associated with nearly all cases of BIA-ALCL. Late onset, persistent seroma around a breast implant represents the classical clinical presentation. Most of the BIA-ALCL patients present with localized disease, which confers an excellent prognosis. Surgical excision is the recommended treatment. For patients with advanced and disseminated diseases, the treatment did not differ from other types of T-cell lymphoma [43].

Therapy of persistent seroma after implant-based reconstruction is lacking robust data. Evacuation of seroma and reinsertion of drainage can be performed, and revision surgery with capsulectomy or implant removal is recommended as the ultima ratio (LoE5/D/AGO+). There is no consensus for the duration of drains, but the consistent data are in favor of drain removal at <30 mL/24 h (LoE2b/B/AGO+) [56].

Neoadjuvant Chemotherapy

If chemotherapy is indicated in patients with EBC, NACT should be considered. Higher pCR rates and improved DFS can be achieved by use of nab-paclitaxel instead of solvent-based paclitaxel (HR positive, TNBC) (LoE1a/A/AGO+). In patients with HER2+ tumors, an anthracycline-/taxane-based (AGO+) or anthracycline-free taxane-/carboplatin regimen (both AGO++) and trastuzumab (adding pertuzumab in nodal positive disease (AGO++) are recommended. In TNBC, dose-dense chemotherapy with an anthracycline/taxane-sequence is the current treatment standard (AGO++). Irrespective of BRCA mutation status the addition of platinum is recommended (cT1/cN+ or cT2, LoE1b/A/AGO+ and from cT1/cN+ or cT2, LoE1a/A/AGO+), due to a significant benefit regarding pCR, DFS and OS [57, 58]. NACT in combination with pembrolizumab, independent of PD-L1 status [59], is a new option if indicated for TNBC patients with cT1c N1-2 or cT2-4 N0-2 (LoE 1b/B/AGO+),

leading to a significantly improved EFS of +7.7% for patients who received a pCR and of +10.6% for the patients who did not respond. Starting with neoadjuvant pembrolizumab, it should always be completed for a further 9 cycles, with pCR (LoE 1b/B/AGO+) and also without pCR (LoE1b/B/AGO++).

Neoadjuvant Endocrine Therapy

NET is suitable for patients who are inoperable or not able or willing to undergo chemotherapy. Selection of endocrine treatment (ET) should be based on the menopausal status and given for at least 4–6 months. Preoperative short-term ET for 2–4 weeks is used to predict the efficacy of ET by the response of Ki-67 (LoE1b/B/AGO+).

Postneoadjuvant Therapy Options

Studies with the use of new therapeutics such as PARPI (OlympiA) and Her2 targeted therapies (e.g., neratinib) can be used both "postneoadjuvant" and in the context of "adjuvant" therapy (see chapter Adjuvant Cytotoxic and Targeted Therapy).

Adjuvant Cytotoxic and Targeted Therapy

Regardless of the subtype, dose-dense anthracycline/taxane-based chemotherapy is still the gold standard for adjuvant chemotherapy. The basis for this is a meta-analysis, which was based on individual patient data [60] and was able to show that dose-dense regimens have a significant advantage with regard to the 10-year recurrence-free survival and mortality compared to conventional schedules. If anthracyclines are not the preferred option, six cycles of an anthracycline-free regimen containing docetaxel/carboplatin are possible (LoE1b/B/AGO+). In TNBC, the question of adding carboplatin in the adjuvant setting is scarce of data (LoE1b/B/AGO+) [61], whereas in the neoadjuvant setting the addition of carboplatin was supported by data from the prospectively randomized Brightness Study [62]. Recently for HER2 negative patients with a high recurrence risk and a germline BRCA1/2 mutation, olaparib demonstrates also after surgery (LoE1b/B/AGO+) and therefore in the adjuvant setting an improved iDFS and OS [11].

In patients with HER2-positive EBC, neoadjuvant treatment with anti-HER2 therapy is preferred (see chapter Neoadjuvant Chemotherapy). Adjuvant trastuzumab is recommended for node negative disease with tumor diameter >5–10 mm, if chemotherapy is recommended (LoE2b/B/AGO+) and highly recommended >10 mm (LoE 1a/A/AGO++). For tumors <2 cm and node negative, 12 × Paclitaxel weekly + trastuzumab for 12 months might be a fair anthracycline free option (LoE2b/B/AGO+). In tumors >2 cm and or node positive, trastuzumab and pertuzumab are recommended as anthracycline-free combinations with docetaxel and carboplatin (LoE1b/A/AGO+) in the classical sequence AC/EC (q3wks or q2wks + G-CSF) followed by a taxane (LoE1a/A/AGO++). The data from the APHINITY-trial support adjuvant pertuzumab in addition to trastuzumab and chemotherapy as preferred in patients with node positive disease in HER2-positive EBC (LoE1b/B/AGO+). At a median follow-up of 74.1 months, invasive DFS in node-positive patients was 87.9% for trastuzumab and pertuzumab versus 83.4% for trastuzumab alone. In the node negative cohort, no additional clinical benefit was evident for the dual blockade (LoE1b/B/AGO+/−).

Extended adjuvant treatment with neratinib in combination with standard endocrine therapy for 12 months showed a significant improvement in iDFS and OS of HR-positive patients who have completed 1 year of trastuzumab-based therapy (LoE1b/B/AGO+). For patients with HR positive EBC, ET according to the menopausal status is the standard of care. The addition of abemaciclib for 2 years to standard ET resulted in an improved 3-year IDFS survival (LoE1b/B/AGO+) [63]. Abemaciclib is indicated in patients with ≥4 positive axillary lymph nodes or 1–3 positive lymph nodes and either G3 or tumor ≥5 cm.

In patients with gBRCA1/2mt presenting with non-pCR (TNBC) after NACT or CPS-EG score ≥3 (HR positive), olaparib is recommended for 1 year in combination with ET (LoE1b/B/AGO+) [10]. Capecitabine is recommended in patients with TNBC and non-pCR (LoE2b/B/AGO+).

Patients with HER2+ disease who did not achieve a pCR received 14 cycles of T-DM1 (LoE1b/B/AGO+) [64]. Additional HER2 targeted therapy with neratinib combined with standard ET can be offered to HR positive patients who have received 12 months of trastuzumab (LoE1b/B/AGO+).

Adjuvant Endocrine Therapy

Endocrine therapy is indicated in all patients with HR positive EBC (LoE1a/A/AGO++). A meta-analysis of the GBG (German Breast Group) of several neoadjuvant trials suggests that tumors with low HR expression (≥1–9%) are biologically similar to TNBC. Thus, omitting endocrine therapy may be an option in cases with very low expression of ER and PR (AGO+) [26]. In case of ER−/PR+ (>10%), immunohistochemical reevaluation of HR should be performed. False positivity for PR should be excluded. Treatment duration of 5 years remains the standard of care. Extended adjuvant treatment (EAT)

might be indicated in patients with an increased risk of relapse, such as G3 or node positive disease at presentation.

If adjuvant chemotherapy is indicated, endocrine therapy should be given sequentially after chemotherapy (LoE2a/B/AGO+). If targeted therapy with T-DM1 antibody drug conjugate is indicated in patients with HER2-overexpressing tumors after neoadjuvant therapy, this treatment can be combined with endocrine therapy simultaneously in patients who also have hormone receptor positive tumors (LoE2b/B/AGO+) [65].

Premenopausal Patients

Premenopausal patients with hormone receptor positive tumors and a low risk of recurrence should be treated with TAM alone for 5 years (LoE1a/A/AGO++) [66]. The AGO commission also recommends in the low-risk ovarian function suppression (OFS) alone if there are contraindications to TAM (LoE1a//B/AGO+). In the light of TAM shortage, this is an additional aspect to be discussed with the patients.

If patients have an increased risk of recurrence (e.g., axillary nodal involvement, high KI67, previous adjuvant or NACT, etc.), we recommend either the combination of OFS for 2–5 years in combination with TAM for 5 years (LoE1a/A/AGO++) or the combination of OFS with an AI (LoE1a/A/AGO++). The recently presented and published meta-analysis from the EBCTCG-Group [67] and the updated meta-analysis of the TEXT and SOFT trials [68] have shown that a combination of OFS with AI for 5 years is also effective and, in some patient groups, even superior to the combination of OFS with TAM. From the EBCTCG meta-analysis the recurrence rate with AI + OFS was 14.7% after 10 years, and 17.5% with TAM + OFS. The breast cancer mortality from the same meta-analysis, showed no difference between the two therapy options (7.2% vs. 6.8%). The recurrence by nodal status was 11.7% with TAM + OFS versus 9.3% with AI + OFS in node negative and 20.9% after TAM + OFS versus 17.1% after AI + OFS in patients with 1–3 involved lymph nodes. From the SOFT and TEXT updated meta-analysis, the absolute improvement in overall survival was 3.3% at 12 years with AI + OFS versus TAM + OFS. The absolute reduction in distant recurrence was 2.6% at 12 years with TAM + OFS versus TAM alone. When counseling premenopausal patients, the combination of OFS with either TAM or AI and their different side effect profiles should be discussed with the patients.

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

In the last year, several studies published their results with the inclusion of CDK 4/6 inhibitors in the adjuvant and postneoadjuvant settings and also with PARPI in patients with germline BRCA1 or 2 mutations. A combination of palbociclib for 1–2 years with standard endocrine therapy in the adjuvant and postneoadjuvant setting did not show any superiority over the standard endocrine therapy and therefore is not recommended in this situation (LoE1b/B/AGO–) [69–72].

We recommend a combination of abemaciclib for 2 years with standard endocrine therapy (LoE1b//B/AGO+) according to the data from the MonarchE study. This combination, newly approved in April 2022, showed a significant improvement in recurrence free and distant disease-free survival (DDFS) compared to standard endocrine therapy alone either given as adjuvant therapy or postneodjuvant therapy for patients with HR positive, HER2 negative, node-positive, high-risk EBC [63].

Within the OlympiA study, the addition of olaparib to standard endocrine therapy increased DFS and DDFS compared to standard endocrine therapy alone [10, 11]. It is to be noted that patients who have hormone receptor positive disease and have been treated with neoadjuvant therapy must have a CPS EG score (breast cancer staging system for assessing prognosis after NACT on the basis of pretreatment clinical stage (CS), estrogen receptor status (E), grade (G), and posttreatment pathologic stage (PS)) of 3 or higher according to the risk calculation of Mittendorf et al. [73] or Marmé et al. [74].

Postmenopausal Patients

The recommendations from 2021 for endocrine adjuvant therapy are still valid. For the majority of patients, this endocrine adjuvant therapy should consist of a sequence for 2–3 years of TAM and 2–3 years of an AI for a total duration of 5 years. The combination of standard endocrine therapy with abemaciclib for 2 years is recommended in postmenopausal patients who have the inclusion criteria of the MonarchE study [63]. The combination of standard endocrine therapy with the PARP inhibitor olaparib for 1 year is recommended in patients with BRCA 1 or 2 germline mutations, who have the inclusion criteria of the OlympiA study [10, 11].

EAT in Premenopausal Women

TAM can be extended for up to 10 years (LoE1a/A/AGO++). EAT with 5 years of TAM should also be offered to those patients with ovarian suppression and TAM or AI for their initial treatment (LoE5/D/AGO+). If the patient is confirmed as being postmenopausal within the first 5 years, endocrine therapy can be continued after 5 years of TAM with 2.5–5 years of letrozole (LoE1b/B/AGO+).

EAT in Postmenopausal Women

After 5 years of TAM, extended therapy with 5 years of TAM is still an option (LoE1a/A/AGO+), but switching to an AI for 2–5years should be preferred (LoE1a/A/

AGO++). If patients receive an AI (upfront or switch), patients at higher risk should be offered 2–5 additional years of AI (LoE1b/B/AGO+).

Osteooncology

Bone-health issues in breast cancer patients are related to treatment of bone metastasis, prevention of metastases, and cancer therapy-induced bone loss. Current AGO recommendations are based on the ESMO Clinical Practice Guideline for bone health in cancer patients [75].

The favorable skeletal effects of denosumab reverse quickly upon its discontinuation because of a vast increase in osteoclast number and activity, which leads to a subsequent profound increase in bone turnover above pre-treatment values, a phenomenon described as the "rebound phenomenon." Therefore, subsequent antiresorptive treatment with a bisphosphonate is mandatory, although the optimal regimen is yet to be clarified [76]. The AGO recommendation is now more specific; bisphosphonates should be given for 1–2 years after discontinuation of denosumab.

Synchronized with the AGO slide-kit update, the ASCO/CCO published a guideline update for the adjuvant use of bisphosphonates and other bone-modifying agents in breast cancer [77]. The benefit of adjuvant bisphosphonates regarding survival is accepted for postmenopausal women irrespective of hormone receptor- or HER2-status. Notably, the NHS PREDICT tool provides estimates of this benefit and may help in decision making processes (https://breast.predict.nhs.uk/). Denosumab (6 × 120 mg/3–4 weeks + 14 × 120 mg/3 months) is not recommended for improvement of prognosis in EBC and stage II/III. For postmenopausal patients undergoing AI therapy, denosumab (60 mg SCq6m) is an option (LoE1b/B/AGO+/−). As adjuvant bone targeted therapy for the improvement of prognosis, clodronate and aminobisphosphonate would be preferred in the postmenopausal situation (LoE1a/A/AGO+). As therapeutic agents and for the improvement of survival, the AGO panel provides a list of recommended bisphosphonates including adjuvant regimens for clodronate, ibandronate, and zoledronic acid.

For therapy of tumor-therapy induced bone loss, bisphosphonates and denosumab are strongly recommended (for both LoE1b/B/AGO++). Optimal duration of bisphosphonate treatment is yet to be defined. Recently, data from the German SUCCESS A-trial were published comparing 2 versus 5 years of treatment with zoledronic acid after adjuvant chemotherapy. At a median of 5 years after the start of zoledronic acid, there were no statistically significant differences observed between the 2- and 5-year arms regarding survival parameters. However, 5 years of treatment was associated with a higher frequency of adverse events versus 2 years of treatment [78]. As a preventive agent, bisphosphonates should be given preference (AGO+) over denosumab (AGO+/−).

Adjuvant Radiotherapy

For adjuvant whole-breast radiotherapy after breast-conserving surgery, moderate hypofractionation represents the standard of care (LoE1a/A/AGO++), while ultra-hypofractionation with 26 Gy in 5 fractions over 1 week or 28.5 Gy in 5 fractions over 5 weeks is considered an option for selected cases (LoE1b/B/AGO+/−) [79]. Premenopausal patients should routinely receive an additional boost of irradiation (LoE1b/B/AGO++), while it should only be used in case of additional risk factors for postmenopausal patients (LoE2b/B/AGO+). Accelerated partial breast irradiation (APBI) with interstitial multicatheter brachytherapy or percutaneous radiotherapy (15 × 2.67 Gy or 5 × 6 Gy) should be considered for patients with early-stage low-risk breast cancer (LoE1b/A/AGO+) [80]. In the absence of additional data from randomized controlled trials, conventional fractionation is still considered the treatment of choice in patients planned for regional nodal irradiation (RNI) (LoE1a/A/AGO++). Moderate hypofractionation can be considered as an alternative (LoE2b/B/AGO+/−). It was clarified that patients with inflammatory breast cancer should always receive postmastectomy radiotherapy (PMRT) and RNI. Patients with ypN+ and/or ypT3-4 should receive PMRT and RNI even if they were initially staged as cT1-2 cN0 (LoE2b/B/AGO+). All other recommendations regarding PMRT and RNI remain unchanged. In the adjuvant setting, olaparib should not be routinely given during radiotherapy due to concerns regarding a possible interaction and a potential increase in toxicity (LoE2b/C/AGO+/−). Further data are needed to establish the safety of concomitant application of PARP-inhibitors and radiotherapy [81, 82].

Breast Cancer: Special Situations

Prognosis of breast cancer during pregnancy is not associated with a worse outcome if adequate treatment is performed (LoE3a). However, there is new evidence that patients diagnosed with breast cancer during lactation and within the first year after pregnancy may have a poorer outcome [83].

The standard endocrine treatment of HR-positive male breast cancer remains TAM. AI in combination with GnRH may also be an effective treatment option (LoE4/C/AGO+) [84]. In general, the ET in male breast

cancer patients should adhere to that in premenopausal women. Fulvestrant (LoE4/C/AGO+/−) and endocrine combination treatment with CDK 4/6 inhibitors (LoE4/C/AGO+/−) may be offered as palliative systemic treatment.

Inflammatory breast cancer should be treated by neoadjuvant systemic treatment. Mastectomy is the surgical standard approach. Delayed breast reconstruction should be preferred (LoE3b/C/AGO+) [85]. Due to the high risk of local recurrence, radiotherapy of the chest wall including regional lymph nodes independent of response to NACT should be performed (LoE2c/B/AGO++) [86].

Ninety-five percent of patients with occult breast cancer present with positive lymph nodes. The standard surgical approach is axillary dissection. However, in case of clinical complete remission after NACT, targeted axillary dissection may be considered to reduce surgical morbidity (LoE3b/C/AGO+/−) [87].

The outcome in secondary angiosarcoma does not seem to be improved by radical surgery. In case tumor-free margins cannot be achieved, breast conserving surgery might be an option [88]. Secondary angiosarcoma does not respond well to chemotherapy. Therefore, the decision for (neo-)adjuvant cytotoxic treatment should be made based on individual risk factors (LoE3a/C/AGO+/−).

The incidence of BIA-ALCL is 1:3,000 in women with textured implants [89]. As written in the chapter of oncoplastic and reconstructive surgery, the standard therapeutic approach is an implant removal combined with a complete capsulectomy including tumorectomy (LoE3a/C/AGO++). The incidence of bilateral BIA-ALCL is 2–4% in patients with bilateral implants; contralateral implant resection should therefore be discussed (LoE4/D/AGO+/−) [90]. In case of extra capsular extension, polychemotherapy e.g., CHOP/CHOEP or Brentuximab-Vedotin-CHP should be administered (LoE4/D/AGO+) [91].

Patients with metaplastic breast carcinoma should receive surgery and axillary staging according to the standard (LoE4/C/AGO++). Metaplastic breast cancer is relatively chemoresistant. To avoid a potential progression during NACT resulting in inoperability, NACT should be avoided (LoE4/C/AGO−) [92].

Breast Cancer – Supportive Care and Side Effect Management

In view of all the new agents and indications, optimal side effect management and supportive care are essential for therapeutic success. In EBC, most side effects of new therapeutic strategies are known from metastasis. In the adjuvant setting, abemaciclib is associated with an iDFS benefit in the curative setting based on monarch-E results. ILD is a rare side effect of CDK 4/6 inhibitor therapy; abemaciclib is associated with a 2.9% incidence (all grades) with only 0.4% >G3 events [93]. In MonarchE, venous thrombotic events with abemaciclib were low with 2.3% of all grades (1.2% G3/4). The incidence is about twice as high with TAM than with an AI as the endocrine backbone.

Interstitial lung disease requires proactive management according to grade and causing agents. The diagnostic work-up should start with chest CT once symptoms arise (LoE1a/B/AGO++). Corticosteroids (starting dose ≥0.5 mg/kg/day prednisolone-equivalent) need to be commenced early (LoE1a/B/AGO++); recommendations for dose holds or therapy discontinuations are detailed in the respective product information.

Hepatitis B screening (HBsAG, anti-HBC, anti-HBs) should be performed before start of adjuvant chemotherapy (LoE2c/B/AGO+); chemotherapy does not need to be interrupted in case of positive serology or reactivation [94]. Proactive and successful side effect management requires a truly interprofessional approach by nursing staff and physicians as well as thorough patient education.

Complementary Therapy and Survivorship

Recently published studies and review articles underline the effects of physical exercise (endurance training three times a week in combination with workout exercises two times a week) on quality of life, cardio-respiratory fitness, physical performance, sleep, pain, depression, lymphedema, and fatigue (LoE1a/A/AGO++) [95]. Evidence is growing that mind-body interventions, including cognitive and behavioral therapies, relaxation techniques, and meditation, improve quality of life among breast cancer patients, and therefore, clinical guidelines include the recommendation (LoE1a/A/AGO). There is growing evidence that acupuncture is effective in improving side effects of breast cancer treatment such as chemotherapy-induced nausea and vomiting (LoE1b/B/AGO+), aromatase-inhibitor induced arthralgia (LoE1a/B/AGO+), cancer pain (LoE1b/B/AGO+), fatigue (LoE1a/B/AGO+), and anxiety and depression (LoE2b/B/AGO+). Some small RCT-studies have shown that melatonin might has beneficial effects in reducing fatigue and depression symptoms and improving sleep quality and cognition for patients (LoE2b/B/AGO+/−). Short-term fasting during NACT has shown improved efficacy of chemotherapy on clinical and pathological level in the multicenter RCT-Phase II DIRECT Trial [96]. Furthermore, trials about short-term fasting during adjuvant chemotherapy and radiation treatment reported less toxicity, reduced fatigue, and improved quality of life in breast cancer patients (LoE2b/AGO+/−). Larger studies

are needed to investigate the effects of fasting during chemotherapy. Before using complementary treatment including phytotherapy, particularly during standard anticancer treatment, possible drug interactions should be excluded.

Gynecological Issues in Breast Cancer Patients/ Contraception

Compared to last year's recommendations, no recommendations have emerged. Systemic hormone replacement therapy to alleviate menopausal symptoms is still contraindicated in breast cancer patients (LoE1b/B/AGO−), while topical vaginal application of low-dose estriol may be used for urogenital symptoms (LoE4/D/AGO+/−). Hot flushes may be treated with serotonin reuptake inhibitors (i.e., venlafaxine LoE1a/A/AGO+). Homeopathy and phytotherapy had no effect on hot flushes in large randomized trials compared with placebo in breast cancer survivors (LoE1b/B/AGO−) [97]. Sleep disturbances might be treated with melatonin (LoE2b/C/AGO+).

To reduce menopausal symptoms in case of unacceptable side effects, a short interruption of endocrine therapy is possible (LoE5/D/AGO+). Physical exercise has positive effects on menopausal symptoms and, to a lesser degree, on the sexuality of patients experiencing treatment-induced menopause (LoE1a/A/AGO++) [98]. Cognitive behavioral therapy is effective in alleviating treatment-induced menopausal symptoms (LoE1b/B/AGO++). Mind-body medicine results in a moderate improvement in hot flushes scores, joint pain, fatigue, and sleep (LoE1b/B/AGO+). There is contradictory data about the effect of acupuncture on hot flushes, depression, and sleep disturbances, but it can be used to treat aromatase-inhibitor induced joint pain (LoE1b/B/AGO+) [99].

Fertility counseling on fertility preservation (https://fertiprotekt.com) should be offered to all patients who wish to retain their fertility (AGO++). Application of GnRH analogues >2 weeks prior to chemotherapy has shown an improved rate of recovery of ovarian function after 2 years (LoE1a/B/AGO+) and might have a moderate effect on preservation of fertility (LoE2a/B/AGO+/−). Low AMH levels seem to be indicative of reduced ovarian reserve in chemotherapy-treated breast cancer patients (LoE1b/B/AGO+).

Hormone-free contraceptive methods are the first choice for patients with breast cancer. Sexual complaints are common in breast cancer patients and should be assessed. Screening tools may help physicians address sexual health issues (LoE4/C/AGO+). Nonhormonal lubricants and moisturizers are the primary treatments for vaginal dryness and dyspareunia (LoE1b/B/AGO+). Microablative fractionated laser or vaginal YAG/Erbium Laser may be an option for some patients to alleviate genital atrophy (LoE2a/A/AGO+/−) [100].

Breast Cancer Follow-Up

Less intensive follow-up for patients with DCIS (clinical examination for all 6 months) versus patients with invasive BC (all 3 months) is recommended. Still, the rationale of breast cancer follow-up is the early detection of curable breast cancer events (LoE1a/B/AGO++). Early detection of symptomatic metastases is desirable (LoE3b/C/AGO+); however, with regard to the early detection of asymptomatic metastases (LoE1a/A/AGO−−), data is inconsistent and, most importantly, does not suggest a survival benefit.

Beyond improvement of survival, additional issues like improvement of quality of life and physical performance and the reduction and early detection of treatment-related side effects are important concerns in this matter (LoE2b/B/AGO+). We added recommendations on cardiologic work-up (echocardiography, BNP measurement in selected cases) in patients treated by anthracyclines/anti-HER2 agents in the adjuvant situation 6, 12, 24 months and yearly up to 5 years after therapy and after the 5th year every 5 years and if the patient is symptomatic according to international guideline [101].

In addition, re-evaluation of current adjuvant therapies (including re-evaluation of menopausal status and change and/or addition of ovarian suppression in high-risk premenopausal patients with chemotherapy-induced amenorrhea) and the assessment or improvement of treatment adherence is an essential part of follow-up care (LoE2b/B/AGO++). Thus, it should be pointed out that every patient has the right to obtain a second opinion (LoE2c/B/AGO++); genetic counseling should be offered if indicated, as should hormone replacement therapy, prophylactic surgery, and breast reconstruction (LoE2c/C/AGO+). Lifestyle modifications such as nightly fasting over 13 h and interventions with regard to comorbidities such as type II diabetes are further important aspects of follow-up.

Most importantly, follow-up examinations of asymptomatic patients in routine situations should not include tumor marker measurements and imaging of any kind. For the detection of curable events, physical and self-examination with MG and adjunctive Us as well as monitoring of treatment toxicity (e.g., of endocrine therapy) are recommended. Follow-up of male breast cancer patients should follow the same procedures as in female breast cancer patients (LoE5/D/AGO+). Unfortunately, there are still no data that would support tailoring breast cancer follow-up according to molecular subtype.

In case of increased risk such as age <50 years, HR negativity, and decreased diagnostic accessibility C/D in MG and US, MRI should be considered [102]. In this context, screening for secondary malignancies according to guidelines is meaningful. Patients and physicians should be aware of the increased risk of hematologic malignancies after chemotherapy and lung cancer after radiotherapy to the breast or chest wall. Further, a DXA scan at baseline and a repeated scan according to individual risk in women with premature ovarian failure or in women on AI therapy are recommended [103].

Health Literacy and Communication

The options for healthy people and patients in cancer prevention and therapy are constantly increasing. At the same time, a change has taken place in the health care system, which strengthens the patients' right of self-determination and embodies in law the informed and shared decision-making process between patients and their doctors, who should no longer make decisions on prevention and treatment concepts alone.

Healthy people as well as patients should be instructed and involved as "experts in their own affairs" during the process of preventing and treating cancer. The main focus is on enabling a self-determined decision on the basis of a sufficiently heathy competence (AGO+) and improving shared decision-making, which depends on successful doctor-patient communication.

Health Literacy

Despite a huge media presence of expert content, it seemed to be difficult for the majority of patients to distinguish between what is really important and how to make the right decisions for coping with illness (health literacy). According to a current survey from 2017, half of all Germans have insufficient or clearly limited health literacy. As a result, numerous initiatives and offers were launched to improve health literacy (Alliance for Health Literacy, National Action Plan Health Literacy). They focus on the special form of the doctor-patient relationship and are based on an overarching set of values: respect for the right of self-determination of the individual, the principle of nonharm, care, and equality.

Communication

Good communication skills are a medical core competence and the basis for a trusting doctor-patient relationship. This in turn has an important influence on the understanding of the disease, cooperation in diagnosis, treatment and rehabilitation, and thus on the success of treatment. "Talking medicine" is becoming increasingly important in the health care system (remuneration) and is offered across sectors as a part of training and continuing education programs for all health care professionals. Qualified training measures can help to promote communicative skills (AGO+).

Shared Decision Making and Patient Decision Aids

Successful communication and the development of a trustful doctor-patient relationship are an important cornerstone for patient participation in the shared decision-making process. The use of decision support in the physician-patient communication (AGO+) will improve knowledge, information and risk perception about treatment options, reduce the decision conflict, increase the feeling about clarity of personal values, encourage an active role in decision making, and improve the match between the chosen option and the patients` values.

These recommendations of the AGO commission presented here show the increasingly rapid development of therapeutic options for early breast carcinoma in recent months and years, based on the excellent data situation in the metastatic situation. At this point, we therefore refer to the recommendations in a separately presented article on MBC.

Conflicts of Interest Statement

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References

1 Empfehlungen Gynäkologische Onkologie kommission mamma, 2021. Available from; www.ago-online.
2 www.cebm.net
3 Lovrics O, Butt J, Lee Y, Lovrics P, Boudreau V, Anvari M, et al. The effect of bariatric surgery on breast cancer incidence and characteristics: a meta-analysis and systematic review. Am J Surg. 2021;222(4):715–22.
4 He Y, Tao Q, Zhou F, Si Y, Fu R, Xu B, et al. The relationship between dairy products intake and breast cancer incidence: a Meta-Analysis of Observational Studies. BMC Cancer. 2021;21(1):1109.
5 Poorolajal J, Heidarimoghis F, Karami M, Cheraghi Z, Gohari-Ensaf F, Shahbazi F, et al. Factors for the primary prevention of breast cancer: a Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021;21(3): e00520.
6 Li C, Fan Z, Lin X, Cao M, Song F, Song F. Parity and risk of developing breast cancer according to tumor subtype: a systematic review and meta-analysis. Cancer Epidemiol. 2021; 75:102050.
7 Ma S, Guo C, Sun C, Han T, Zhang H, Qu G, et al. Aspirin use and risk of breast cancer: a Meta-analysis of Observational Studies from 1989 to 2019. Clin Breast Cancer. 2021;21(6): 552–65.
8 https: //www.onkozert.de/informationen-zertifizierung/hinweise-downloads/genetische-beratung-familiaeres-mammakarzinom/checkliste_erbliche_belastung_brust_gyn-210212.
9 NICE (National Institute for Health and Care Excellence) guidance: Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clinical guideline [CG164]. Published: 25 June 2013 Last updated: 20 November 2019.
10 Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med. 2021;384(25): 2394–405.
11 Tutt ANJ, Garber J, Gelber RD, Phillips KA, Eisen A, Johannsson OT, et al. Pre-specified event driven analysis of overall survival (OS) in the olympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. Ann Oncol. 2022.Pages ESMO Virtual Plenary VP1-2022
12 Dorling L, Carvalho S, Allen J, Allen J, González-Neira A, Luccarini C, et al. Breast cancer risk genes: association analysis in more than 113,000 women. N Engl J Med. 2021 Feb 4;384(5):428–39.
13 Tischkowitz M, Balmaña J, Foulkes WD, James P, Ngeow J, Schmutzler R, et al. Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8): 1416–23.
14 Gao C, Polley EC, Hart SN, Huang H, Hu C, Gnanaolivu R, et al. Risk of breast cancer among carriers of pathogenic variants in breast cancer predisposition genes varies by polygenic risk score. J Clin Oncol. 2021 Aug 10;39(23):2564–73.
15 https: //healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/screening-ages-and-frequencies.
16 Alabousi M, Zha N, Salameh JP, Samoilov L, Sharifabadi AD, Pozdnyakov A, et al. Digital breast tomosynthesis for breast cancer detection: a diagnostic test accuracy systematic review and meta-analysis. Eur Radiol. 2020 Apr; 30(4):2058–71.
17 Alabousi M, Wadera A, Kashif Al-Ghita M, Kashef Al-Ghetaa R, Salameh JP, Pozdnyakov A, et al. Performance of digital breast tomosynthesis, synthetic mammography, and digital mammography in breast cancer screening: a systematic review and meta-analysis. Natl Cancer Inst. 2021 Jun 1;113(6):680–90.
18 Heywang-Köbrunner SH, Jänsch A, Hacker A, Weinand S, Vogelmann T. Digital breast tomosynthesis (DBT) plus synthesised two-dimensional mammography (s2D) in breast cancer screening is associated with higher cancer detection and lower recalls compared to digital mammography (DM) alone: results of a systematic review and meta-analysis. Eur Radiol. 2021 Oct 25;32(4):2301–12.
19 Veenhuizen SGA, de Lange SV, Bakker MF, Pijnappel RM, Mann RM, Monninkhof EM, et al. Supplemental breast MRI for women with extremely dense breasts: results of the second screening round of the DENSE trial. Radiology. 2021;299(2):278–86.
20 Hadadi I, Rae W, Clarke J, McEntee M, Ekpo E. Diagnostic performance of adjunctive imaging modalities compared to mammography alone in women with non-dense and dense breasts: a systematic review and meta-analysis. Clin Breast Cancer. 2021 Aug;21(4):278–91.
21 Ko MJ, Park DA, Kim SH, Ko ES, Shin KH, Lim W, et al. Accuracy of digital breast tomosynthesis for detecting breast cancer in the diagnostic setting: a systematic review and meta-analysis. J Radiol. 2021 Aug;22(8):1240–52.
22 Cozzi A, Magni V, Zanardo M, Schiaffino S, Sardanelli F. Contrast-enhanced mammography: a systematic review and meta-analysis of diagnostic performance. Radiology. 2021 Dec 14;302(3):568–81.
23 Schünemann HJ, Lerda D, Quinn C, Follmann M, Alonso-Coello P, Rossi PG, et al. Breast cancer screening and diagnosis: a synopsis of the European breast guidelines. Ann Intern Med. 2020;172(1):46–56.
24 Le Boulc'h M, Gilhodes J, Steinmeyer Z, Molière S, Mathelin C. Pretherapeutic imaging for axillary staging in breast cancer: a systematic review and meta-analysis of ultrasound, MRI and FDG PET. Clin Med. 2021 Apr 6;10(7):1543.
25 Mariscotti G, Durando M, Tagliafico A, Campanino PP, Bosco D, Casella C, et al. : Preoperative breast cancer staging with multi-modality imaging and surgical outcomes. Eur J Radiol. 2020 Jan;122:108766. Epub 2019 Nov 22. Erratum in: Eur J Radiol. 2020 Feb 26; 108919.
26 Villegas SL, Nekljudova V, Pfarr N, Engel J, Untch M, Schrodi S, et al. Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors: an analysis of 2765 patients from neoadjuvant clinical trials. Eur J Cancer. 2021;148: 159–70.
27 Dieci MV, Griguolo G, Bottosso M, Tsvetkova V, Giorgi CA, Vernaci G, et al. Impact of estrogen receptor levels on outcome in non-metastatic triple negative breast cancer patients treated with neoadjuvant/adjuvant chemotherapy. NPJ Breast Cancer. 2021 Aug 2; 7(1):101.
28 Mills AM, Gottlieb CE, Wendroth SM, Brenin CM, Atkins KA. Pure apocrine carcinomas represent a clinicopathologically distinct androgen receptor-positive subset of triple-negative breast cancers. Am J Surg Pathol. 2016 Aug;40(8):1109–16.
29 Montagna E, Cancello G, Pagan E, Bagnardi V, Munzone E, Dellapasqua S, et al. Prognosis of selected triple negative apocrine breast cancer patients who did not receive adjuvant chemotherapy. Breast. 2020 Oct;53:138–42.
30 Saridakis A, Berger ER, Harigopal M, Park T, Horowitz N, Le Blanc J, et al. Apocrine breast cancer: unique features of a predominantly triple-negative breast cancer. Ann Surg Oncol. 2021 Oct;28(10):5610–6.
31 Wetterskog D, Lopez-Garcia MA, Lambros MB, A'Hern R, Geyer FC, Milanezi F, et al. Adenoid cystic carcinomas constitute a genomically distinct subgroup of triple-negative and basal-like breast cancers. J Pathol. 2012 Jan;226(1):84–96.
32 Martelotto LG, De Filippo MR, Ng CK, Natrajan R, Fuhrmann L, Cyrta J, et al. Genomic landscape of adenoid cystic carcinoma of the breast. J Pathol. 2015 Oct;237(2):179–89.
33 Del Castillo M, Chibon F, Arnould L, Croce S, Ribeiro A, Perot G, et al. Secretory breast carcinoma: a histopathologic and genomic spectrum characterized by a joint specific ETV6-NTRK3 gene fusion. Am J Surg Pathol. 2015 Nov;39(11):1458–67.
34 Trihia HJ, Valavanis C, Novkovic N, Koutsodontis G, Petraki M, Efstathiou E. Polymorphous adenocarcinoma of the breast-an exceptionally rare entity: clinicopathological description of a case and brief review. Breast J. 2020 Feb;26(2):261–4.
35 Lozada JR, Basili T, Pareja F, Alemar B, Paula ADC, Gularte-Merida R, et al. Solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid neoplasms (solid papillary carcinomas with reverse polarity) harbour recurrent mutations affecting IDH2 and PIK3CA: a validation cohort. Histopathology. 2018 Aug;73(2):339–44.

36 Sinn P, Brucker SY, Budach W, et al. DCIS und Risikoläsionen. In: Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms (Hrsg: Leitlinienprogramm Onkologie der AWMF, DKG und DKH); 2017. p. 79–89.
37 Wahab RA, Lee SJ, Mulligan ME, Zhang B, Mahoney MC. Upgrade rate of pure flat epithelial atypia diagnosed at core needle biopsy: a systematic review and meta-analysis. Radiol Imaging Cancer. 2021 Jan 22;3(1):e200116.
38 Khan S, Diaz A, Archer KJ, Lehman RR, Mullins T, Cardenosa G, et al. Papillary lesions of the breast: to excise or observe? Breast J. 2018 May;24(3):350–5.
39 Rageth CJ, O'Flynn EAM, Pinker K, Kubik-Huch RA, Mundinger A, Decker T, et al. Second international consensus conference on lesions of uncertain malignant potential in the breast (B3 lesions). Review, Breast Cancer Res Treat. 2018;174(2):279–96.
40 DeCensi A, Puntoni M, Guerrieri-Gonzaga A, Caviglia S, Avino F, Cortesi L, et al. Randomized placebo controlled trial of low-dose TAM to prevent local and contralateral recurrence in breast intraepithelial neoplasia. J Clin Oncol. 2019 Jul 1;37(19):1629–37.
41 Wang H, Zhang S, Yee D, Pinker K, Kubik-Huch RA, Mundinger A, et al. Impact of body mass index on pathological complete response following neoadjuvant chemotherapy in operable breast cancer: a metaanalysis. Breast Cancer. 2021;28(3):616–29.
42 Hovis K, Mercaldo S, Kim G, Lamb LR, Oseni TO, Bahl M. Contralateral breast cancer after curative-intent treatment for ductal carcinoma in situ: Rate and associated clinicopathological and imaging risk factors. Clin Imaging. 2022 Nov 20;82:179–92.
43 Nelson JA, McCarthy C, Dabic S, Polanco T, Chilov M, Mehrara BJ, et al. BIA-ALCL and textured breast implants: a systematic review of evidence supporting surgical risk management strategies. Plast Reconstr Surg. 2021 May 1;147(5 Suppl):7S–13S.
44 Canelo-Aybar C, Taype-Rondan A, Zafra-Tanaka JH, Rigau D, Graewingholt A, Lebeau A, et al. Preoperative breast magnetic resonance imaging in patients with ductal carcinoma in situ: a systematic review for the European Commission Initiative on Breast Cancer (ECIBC). Eur Radiol. 2021 Aug;31(8):5880–93.
45 Grimm L, Rahbar H, Abdelmalak M, Hall AH, Ryser MD. Ductal carcinoma in situ: state-of-the-art review radiology. Radiology. 2021 Dec 21;302(2):246–55.
46 Lei RY, Carter DL, Antell AG, Nowels MA, Tole SP, Bennett JP, et al. A comparison of predicted ipsilateral tumor recurrence risks in patients with ductal carcinoma in situ of the breast after breast-conserving surgery by breast radiation oncologists, the Van Nuys Prognostic Index, the Memorial Sloan Kettering Cancer Center DCIS Nomogram, and the 12-gene DCIS score assay. Adv Radiat Oncol. 2020;6(2):100607.
47 Wärnberg F, Karlsson P, Holmberg E, Sandelin K, Whitworth PW, Savala J, et al. Prognostic risk assessment and prediction of radiotherapy benefit for women with ductal carcinoma in situ (DCIS) of the breast, in a randomized clinical trial (SweDCIS). Cancers. 2021;13:6103.
48 Athanasiou C, Mallidis E, Tuffaha H. Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis. Eur J Surg Oncol. 2022;48(1):53–9.
49 Barrio AV, Montagna G, Mamtani A, Sevilimedu V, Edelweiss M, Capko D, et al. Nodal recurrence in patients with node-positive breast cancer treated with sentinel node biopsy alone after neoadjuvant chemotherapy: a rare event. JAMA Oncol. 2021;7(12):1851–5.
50 Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol. 2016;34(10):1072–8.
51 Banys-Paluchowski M, Gasparri ML, de Boniface J, Gentilini O, Stickeler E, Hartmann S, et al. Surgical management of the axilla in clinically node-positive breast cancer patients converting to clinical node negativity through neoadjuvant chemotherapy: current status, knowledge gaps, and rationale for the EUBREAST-03 AXSANA Study. Cancers. 2021;13(7):1565.
52 Weber WP, Soysal SD, El-Tamer M, Sacchini V, Knauer M, Tausch C, et al. First international consensus conference on standardization of oncoplastic breast conserving surgery. Breast Cancer Res Treat. 2017 Aug;165(1):139–49.
53 Weber WP, Morrow M, Boniface J, Pusic A, Montagna G, Kappos EA, et al. Knowledge gaps in oncoplastic breast surgery. Lancet Oncol. 2020 Aug;21(8):e375–85.
54 Hai Y, Chong W, Lazar MA. Extended prophylactic antibiotics for mastectomy with immediate breast reconstruction: a meta-analysis. Plast Reconstr Surg Glob Open. 2020 Jan 27;8(1):e2613.
55 Hallberg H, Rafnsdottir S, Selvaggi G, Strandell A, Samuelsson O, Stadig I, et al. Benefits and risks with acellular dermal matrix (ADM) and mesh support in immediate breast reconstruction: a systematic review and meta-analysis. J Plast Surg Hand Surg. 2018 Jun;52(3):130–47.
56 Scomacao I, Cummins A, Roan E, Duraes EFR, Djohan R. The use of surgical site drains in breast reconstruction: A systematic review. J Plast Reconstr Aesthet Surg. 2020 Apr;73(4):651–62.
57 Feng W, He Y, Xu J, Zhang H, Si Y, Xu J, et al. A meta-analysis of the effect and safety of platinum-based neoadjuvant chemotherapy in treatment of resectable triple-negative breast cancer. Anticancer Drugs. 2022 Jan 1;33(1):e52–60.
58 Li J, Chen L, Tan W, Qi F, Zhang Y, Wang Z, et al. Platinum is essential in neoadjuvant treatment of triple-negative breast cancer: a network meta-analysis. Cancer Biol Med. 2022 Feb 16.
59 Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kümmel S, et al. KEYNOTE-522 investigators. Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med. 2022 Feb 10;386(6):556–67.
60 Early Breast Cancer Trialists' Collaborative Group. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019;393(10179):1440–52.
61 Yu KD, Ye FG, He M, Fan L, Ma D, Mo M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer. A phase 3 randomized clinical trial. JAMA Oncol. 2020 Sep 1;6(9):1390–6.
62 Geyer CE, Sikov WM, Huober J, Rugo HS, Wolmark N, O'Shaughnessy J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022 Apr;33(4):384–94.
63 Harbeck N, Rastogi P, Martin M, Tolaney SM, Shao ZM, Fasching PA, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021 Dec;32(12):1571–81.
64 von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019;380(7):617–28.
65 Loibl S, Chiun-Sheng H, Mano MS, Mamounas TP, Geyer CE, Untch M, et al. Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (T) in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analysis from KATHERINE. ESMO Breast. 2020;32(8):1005–14.
66 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant TAM: patient-level meta-analysis of randomised trials. Lancet. 2011;378:771–84.
67 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022 Mar;23(3):382–92.
68 Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Láng I, et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression (OFS) versus TAM + OFS versus TAM in premenopausal women with HR + early breast : update of the TEXT and SOFT trials. SABCS. 2021:GS2–05.

69 Mayer EL, Dueck AC, Martin M, Rubovszky G, Burstein HJ, Bellet-Ezquerra M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2021;22(2):212–22.

70 Loibl S, Marmé F, Martin M, Untch M, Bonnefoi H, Kim SB, et al. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancerand with high relapse risk after neoadjuvant chemotherapy (NACT): First results from PENELOPE-B. San Antonio Breast Cancer Symposium. 2020;2020:GS1–02.

71 Loibl S Gnant M, Dueck AC, Frantal S, Martin M, Burstein HJ, Greil R, et al. Adjuvant palbociclib for early breast cancer: the PALLAS trial results (ABCSG-42/AFT-05/BIG-14-03). J Clin Oncol. 2021 Dec 7;40(3):282–93.

72 Loibl S, Marmé F, Martin M, Untch M, Bonnefoi H, Kim SB, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer: the penelope-B tTrial. J Clin Oncol. 2021 May 10;39(14):1518–30.

73 Mittendorf EA, Jeruss JS, Tucker SL, Kolli A, Newman LA, Gonzalez-Angulo AM, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. J Clin Oncol. 2011 May 20;29(15):1956–62.

74 Marmé F, Lederer B, Blohmer JU, Costa SD, Denkert C, Eidtmann H, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer. 2016 Jan;53:65–74.

75 Coleman R, Hadji P, Body JJ, Santini D, Chow E, Terpos E, et al. Bone health in cancer: ESMO clinical practice guidelines. Ann Oncol. 2020;31:1650–63.

76 Anastasilakis AD, Makras P, Yavropoulou MP, Tabacco G, Naciu AM, Palermo A. Denosumab discontinuation and the rebound phenomenon: a narrative review. Jcm. 2021;10(1):152.

77 Eisen A, Somerfield MR, Accordino MK, Blanchette PS, Clemons MJ, Dhesy-Thind S, et al. Use of adjuvant bisphosphonates and other bone-modifying agents in breast cancer: ASCO-OH (CCO) guideline update. J Clin Oncol. 2022;40:787–800.

78 Friedl TWP, Fehm T, Müller V, Lichtenegger W, Blohmer J, Lorenz R, et al. Prognosis of patients with early breast cancer receiving 5 years vs 2 years of adjuvant bisphosphonate treatment: a phase 3 randomized clinical trial. JAMA Oncol. 2021;7:1149–57.

79 Krug D, Baumann R, Combs SE, Duma MN, Dunst J, Feyer P, et al. Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward. Strahlenther Onkol. 2021;197:269–80.

80 Strnad V, Krug D, Sedlmayer F, Piroth MD, Budach W, Baumann R, et al. DEGRO practical guideline for partial-breast irradiation. Strahlenther Onkol. 2020;196:749–63.

81 Jagsi R, Griffith KA, Bellon JR, Woodward WA, Horton JK, Ho A, et al. Concurrent veliparib with chest wall and nodal radiotherapy in patients with inflammatory or locoregionally recurrent breast cancer: The TBCRC 024 Phase I Multicenter Study. J Clin Oncol. 20182017;77:266–8.

82 Loap P, Loirat D, Berger F, Cao K, Ricci F, Jochem A, et al. Combination of olaparib with radiotherapy for triple-negative breast cancers: one-year toxicity report of the RADIOPARP phase I trial. Int J Cancer. 2021;149:1828–32.

83 Lefrère H, Floris G, Schmidt MK, Neven P, Warner E, Cardonick E, et al. Data describing the poor outcome associated with a breast cancer diagnosis in the post-weaning period. Data Brief. 2021;38:107354.

84 Reinisch M, Seiler S, Hauzenberger T, Kamischke A, Schmatloch S, Strittmatter HJ, et al. Efficacy of endocrine therapy for the treatment of breast cancer in men: results from the MALE phase 2 randomized clinical trial. JAMA Oncol. 2021;7(4):565–72.

85 Adesoye T, Lucci A. Current surgical management of inflammatory breast cancer. Ann Surg Oncol. 2021;28(10):5461–7.

86 Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, et al. NCCN guidelines® insights: breast cancer, version 4.2021. J Natl Compr Canc Netw. 2021;19(5):484–93.

87 Botty Van den Bruele A, Lavery J, Plitas G, Pilewskie ML. Axillary downstaging in occult primary breast cancer after neoadjuvant chemotherapy. Ann Surg Oncol. 2021;28(2):968–74.

88 Cohen-Hallaleh RB, Smith HG, Smith RC, Stamp GF, Al-Muderis O, Thway K, et al. Radiation induced angiosarcoma of the breast: outcomes from a retrospective case series. Clin Sarcoma Res. 2017;7:15.

89 De Jong WH, Panagiotakos D, Proykova A, Samaras T, Clemens MW, De Jong D, et al. Final opinion on the safety of breast implants in relation to anaplastic large cell lymphoma: report of the scientific committee on health, emerging and environmental risks (SCHEER). Regul Toxicol Pharmacol. 2021;125:104982.

90 DeCoster RC, Lynch EB, Bonaroti AR, Webster JM, Butterfield TA, Evers BM, et al. Breast implant-associated anaplastic large cell lymphoma: an evidence-based systematic review. Ann Surg. 2021;273(3):449–58.

91 Stack A, Ali N, Khan N. Breast implant-associated anaplastic large cell lymphoma: a review with emphasis on the role of brentuximab vedotin. J Cell Immunol. 2020;2(3):80–9.

92 Wong W, Brogi E, Reis-Filho JS, Plitas G, Robson M, Norton L, et al. Poor response to neoadjuvant chemotherapy in metaplastic breast carcinoma. NPJ Breast Cancer. 2021;7(1):96.

93 Raschi E, Fusaroli M, Ardizzoni A, Poluzzi E, De Ponti F. Cyclin-dependent kinase 4/6 inhibitors and interstitial lung disease in the FDA adverse event reporting system: a pharmacovigilance assessment. Breast Cancer Res Treat. 2021 Feb;186(1):219–27.

94 Hwang JP, Feld JJ, Hammond SP, Wang SH, Alston-Johnson DE, Cryer DR, et al. Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO provisional clinical opinion update. J Clin Oncol. 2020;38:3698–715.

95 Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Komplementärmedizin in der Behandlung von onkologischen PatientInnen, Langversion 1.1, 2021, AWMF Registernummer: 032/055OL. Available from: https://www.leitlinienprogramm-onkologie.de/leitlinien/komplementaermedizin/.

96 DeGroot S, Lugtenberg RT, Cohen D, Welters MJP, Ehsan I, Vreeswijk MPG, et al. Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trail. Nat Commun. 2020;11:3083.

97 Heudel PE, Van Praagh-Doreau I, Duvert B, Cauvin I, Hardy-Bessard AC, Jacquin JP, et al. Does a homeopathic medicine reduce hot flushes induced by adjuvant endocrine therapy in localized breast cancer patients? A multicenter randomized placebo-controlled phase III trial. Support Care Cancer. 2019;27:1879–89.

98 Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity for women with breast cancer after adjuvant therapy. Cochrane Database Syst Rev. 2018;1:Cd011292.

99 Hershman DL, Unger JM, Greenlee H, Capodice JL, Lew DL, Darke AK, et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women ith early-stage breast cancer: a randomized clinical trial. Jama. 2018;320:167–76.

100 Athanasiou S, Pitsouni E, Douskos A, Salvatore S, Loutradis D, Grigoriadis T. Intravaginal energy-based devices and sexual health of female cancer survivors: a systematic review and meta-analysis. Lasers Med Sci. 2019;35(1):1.

101 Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020;31:171–90.

102 Shah C, Ahlawat S, Khan A, Tendulkar RD, Wazer DE, Shah SS, et al. The role of MRI in the follow-up of women undergoing breast-conserving therapy. Am J Clin Oncol. 2016 Jun;39(3):314–9.

103 Runowcz CD, Leach CR, Henry L, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. CA Cancer J Clin. 2016;66:43–73.