Update 2010 of the German AGO Recommendations for the Diagnosis and Treatment of Early and Metastatic Breast Cancer – Chapter A: Surgery, Pathology and Prognostic Factors, Adjuvant and Neoadjuvant Therapy, Adjuvant Radiotherapy

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Introduction

For the last 9 years, the Breast Committee of the German Gynecological Oncology Group (AGO) has published annually updated and evidence-based recommendations for the diagnosis and treatment of early and metastatic breast cancer. By now, these guidelines are well established and widely used by breast cancer specialists in and outside of Germany. The rating of evidence was performed according to the Oxford group proposals of levels of evidence (LoE; www.cebm.net) [1], whilst the AGO recommendations were made according to a well defined scale (AGO +/-; table 1). In addition, we

published a patients' version of these recommendations in order to provide patients with the same information as their physicians. Here, we report on the 2010 update of the AGO recommendations. The full version of these guidelines is available as a PDF slide file at www.ago-online.de ('Leitlinien') [2]. We focus on differences to the 2009 recommendations, i.e. on updated and new recommendations with regard to surgery, pathology and prognostic factors, adjuvant and neoadjuvant therapy, and adjuvant radiotherapy.

Breast Cancer Surgery

Oncologic Aspects

A thorough preoperative diagnostic work-up including preoperative histology by image-directed needle biopsy and a detailed description of the extent of the suspicious lesion are required for planning breast surgery (LoE 2a B, AGO +/-). However, evidence is accumulating that routine magnetic resonance imaging (MRI) of the breast, even in the case of invasive lobular cancer, may not be beneficial since it causes more extensive breast surgery in a substantial proportion of women without providing any survival advantage (LoE 2b B, AGO +/-). Randomized controlled trials (RCTs) are needed to determine the clinical value of detecting additional disease that changes surgical treatment in women with apparently localized breast cancer. MRI is only recommended in patients with hereditary disease (LoE 4 C, AGO +).

History and physical examination are good clinical practice and mandatory in every patient. Chest X-ray, liver ultrasound,

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Table 1. AGO grades of recommendation, from Kommission ‘Mamma’ der Arbeitsgemeinschaft für Gynäkologische Onkologie e.V. (AGO) Guidelines 2010, Version 1.1 (www.ago-online.de [2])

+/+	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.

and bone scan have been used for the initial staging of breast cancer. However, these routine staging procedures may be beneficial for decision making only in patients at high risk for early metastasis, but not in low-risk breast cancer (clinically T1 and N0) (LoE 5 D, AGO +).

Axillary dissection is mainly a diagnostic procedure. Removal of tumor-free lymph nodes increases morbidity and has no prognostic impact. Available evidence suggests that quality-assured sentinel lymph node excision (SLNE) is a reliable predictor for axillary lymph node status with high levels of sensitivity (90–95%), specificity (100%), negative predictive value (95%), and accuracy (97%). SLNE has become a standard surgical procedure in patients with clinically and sonographically negative axillae (cN0). Nowadays, the concept of SLNE is proven in many indications (e.g. cT2, multicentricity). In large ductal carcinomas in situ (DCIS), or if mastectomy is required due to DCIS, SLNE should be offered to the patient. For SLNE before or after neoadjuvant chemotherapy (NACT), a prospective study, the SENTINA trial, is currently performed in Germany. In male breast cancer patients, SLNE is also feasible and accurate in clinically node-negative disease.

There are only few reports about SLNE during pregnancy. The radioactive dosage of the applied radiocolloid is estimated to be very low and therefore not harmful for the fetus. Nothing is known about altered lymph drainage during pregnancy. In a letter to one of the authors (I.B.), the Bundesamt für Strahlenschutz stated that no fetal harm is expected after application of 11 MBq on the day of surgery and that therefore no indication for termination of pregnancy is given. By performing an SLNE biopsy, a large proportion of patients with pregnancy-associated breast cancer may be spared the risk of a complete axillary lymph node dissection. Therefore, we also recommend the procedure as an option during pregnancy (LoE 3 C, AGO +).

In order to enable SLNE in patients with axillary lymph nodes that are suspicious according to clinical and sonographic assessment, histological diagnosis can be performed by fine needle biopsy or core biopsy of that node (LoE 3b C, AGO +/-).

The standard surgical procedure for early breast cancer is breast conservation followed by radiation therapy. Ipsilateral breast tumor relapse rates should be lower than 10% after

10 years of follow-up. Randomized trials and clinical series of breast conservation report conflicting evidence relating to tumor size as a risk factor for local recurrence, although most studies report no association. There is little evidence to justify the use of tumor size alone as an exclusion criterion for breast conservation therapy. Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy. Skin-sparing mastectomy (SSM) with or without conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe treatment option in selected patients. Survival rates after modified radical mastectomy are equivalent to those after radical mastectomy according to Rotter-Halsted.

Excisional biopsy should be wire-guided if the lesion is not palpable, and specimen radiography should be performed. Radioguided occult lesion localization (ROLL) is a possible alternative to the commonly used wire-guided localization (WGL) of non-palpable breast lesions. Intratumoral injection of a radiotracer identifies both the primary tumor and the sentinel lymph nodes for intraoperative gamma probe-guided dissection. Intraoperative radiography or ultrasound are indicated in all cases of non-palpable lesions (Good Clinical Practice, GCP). In breast-conserving surgery, the margins of the specimen have to be tumor-free. There is no universal agreement on the width of the tumor-free margin. Re-excision is required for a close margin < 1 mm (for DCIS < 2 mm) in paraffin section. Re-excision is recommended within a period of < 4 weeks. Patients with involved margins, large tumor size, and/or a DCIS component are more likely to have residual disease on re-excision.

Plastic Reconstructive Aspects after Mastectomy

Recent publications concerning breast reconstruction (BR) deal with immediate reconstruction and related complications in general, and particularly due to postoperative radiotherapy. A second topic is implant BR and the use of titanized mesh, acellular dermis, and lipofilling to enhance and improve implant coverage. The controversy among advocates of the different methods of autologous BR (DIEP (deep inferior epigastric perforator) flap versus pedicled TRAM (transverse rectus abdominis myocutaneous; pTRAM)) continues without demonstrating an advantage of either method. The role of a so-called ‘delay’ is still under investigation.

Surgical complications and the use of neoadjuvant bevacizumab was the topic of an oral presentation at the San Antonio Breast Cancer Conference 2009 with the conclusion that the use of tissue expanders could be problematic in patients treated with anti-angiogenesis therapy [3].

Kronowitz [4] from the M. D. Anderson Cancer Center in Houston, Texas, states an increasing acceptance of the so-called 'delayed-immediate breast reconstruction' in patients who desire BR and face the possibility of postmastectomy radiotherapy (PMRT). Using an expander for immediate BR after SSM as an adjustable scaffold helps to preserve the 3-dimensional shape of the breast skin envelope: if PMRT is not necessary, the patient can proceed with the initially intended method of BR; otherwise PMRT will be performed followed by expander removal and autologous BR.

In SSM and immediate BR, titanized extralight mesh (TiLOOP Bra[®], PFM Medical AG, Köln, Germany) and acellular dermal matrix (ADM; Epiflex[®], German Institute for Cellular and Tissular Replacement (DIZG), Berlin, Germany) are able to extend the necessary extent of the implant pocket and facilitate positioning of the implant. In the case of ADM, the thickness of the overlying tissue is enhanced while at the same time reducing the risk of wrinkling, a goal that can also be achieved with lipofilling as long as it is administered in small portions strictly to the subdermal layer.

A great number of publications still deal with autologous BR – mostly DIEP and free TRAM, but also SIEA (superficial inferior epigastric artery), TMG (transverse myocutaneous gracilis) and GAP (gluteal artery perforator) flaps. Most DIEP publications discuss preoperative computed tomography (CT) angiographic methods to reduce complications and operating room time, and clinical flap-monitoring procedures. Peeters et al. [5] advise using ultrasound as a tool to detect fat necrosis, thereby adding another 35% to the clinically diagnosed 14%. Two publications with substantial numbers of patients deal with pTRAM (Kim et al. [6], 500 flaps) and good results [6]. Chun et al. [7] conclude presenting 105 bipediced TRAMs: 'Bilateral pedicled TRAM flaps ... remain a safe and reliable procedure, with donor-site morbidity rates that are comparable to those of other BR techniques'. Atisha et al. [8] from Ann Arbor, Michigan, add new insight to the surgical delay procedure in pTRAM. Due to a retrospective cohort study on 112 pTRAMs the authors conclude that with a significant *p* value of 0.018 the delay group had definitively less ischemic complications (6.6%) than the non-delay group with 17.6%.

Pathology and Prognostic Factors

Pathology

A modification was introduced into the pathology guidelines in order to cover the issue of adequate biopsy material for determining the HER2 status. It was reported that false-positive

or -negative immunohistochemical labeling may occur in core biopsies. Discrepancy rates between 12 and 25% were found [9, 10]. In a validation study done at Hannover Medical School on 533 breast cancer specimens with parallel HER2 analysis in the core biopsy and resection specimen, a concordance rate of 95% was established, exceeding the concordance rate for progesterone receptor (PR) (89%; estrogen receptor (ER) 98%). The discrepant cases included 4 with inter-observer disagreement that was corrected by review, 2 with DCIS labeling in the core biopsy, and 2 bifocal tumors (von Wasielewski and Kreipe, unpublished).

It is recommended that individual laboratories should validate their methods by parallel staining of core biopsies and resection specimens before immunohistochemical detection of HER2 is done on a routine basis on core biopsies (LoE 5 D, AGO +/+). Attention needs to be paid to background staining in core biopsies, and tumor HER2 staining should be evaluated by comparison with staining of normal duct epithelium. If a $\geq 95\%$ concordance is achieved, the method could be considered validated. An alternative approach would be to reanalyze all G1 and G2 cases with HER2 3+ in core biopsies either by *in situ* hybridization (ISH) or by parallel staining of the resection specimen. In the case of a discrepancy between core biopsy and specimen, the HER2 overexpressing sample should be re-evaluated by a different method, either ISH or immunohistochemistry. If the discrepancy persists, HER2-directed treatment could be considered if amplification is proven in at least one of the two samples.

Prognostic and Predictive Factors

In 2009, only a few study results regarding prognostic and predictive factors were presented that may have an additional impact on daily breast cancer patient care. A prospective cohort study of 1,897 breast cancer survivors diagnosed between 1997 and 2000 with a mean follow-up of 5.9 years suggested that regular alcohol intake of at least half a drink or more per day is associated with an increased risk of recurrence (hazard rate (HR) 1.34, 95% confidence interval (CI) 1.0–1.82; *p* = 0.04) and death from breast cancer (HR 1.51, 95% CI 1.0–2.28; *p* = 0.05), particularly among postmenopausal and overweight/obese women (LoE 2b B, AGO +). However, confirmation in other large prospective studies is needed before any definite lifestyle recommendations can be made [11]. In addition, with a follow-up of 10 years, it was shown in 18,967 women from the Danish Breast Cancer Cooperative Group database that after adjustment for other prognostic factors, patients with a body mass index (BMI) over 25 had a significantly increased risk (42–46%) of developing distant metastases and a significantly increased risk (26–38%) of dying from breast cancer (LoE 2b B, AGO +). Adjuvant treatment seemed less effective in patients with a BMI of at least 30 [12].

Adjuvant Systemic Therapy

Adjuvant Chemotherapy (Optimal Drugs / Optimal Dosage / Trastuzumab)

Anthracyclines and taxanes are essential parts of adjuvant chemotherapy in primary breast cancer. In node-positive disease, taxanes are an evidence-based standard. In node-negative disease, taxanes need to be considered in patients at high risk for relapse (LoE 2b B, AGO +) as the GEICAM 9805 trial showed a significant improvement in disease-free survival for DocAC (docetaxel, doxorubicin, cyclophosphamide) vs. FAC (5-fluorouracil, doxorubicin, cyclophosphamide). If considering all risks (e.g. cardiac toxicity, secondary leukemia), and an anthracycline-containing regimen seems to be contraindicated, the anthracycline-free combination DocC is an evidence-based option [13]. However, the comparator arm in the US Oncology trial was merely 4 × AC. Thus, participation in ongoing clinical trials (e.g. Plan B, SUCCESS C) which are currently evaluating non-anthracycline regimens in comparison to standard triplet combinations or anthracycline-taxane sequences is strongly recommended. In high-risk node-positive disease with > 4 involved lymph nodes, the dose-dense, dose-intensified ddETC (epirubicin, paclitaxel, cyclophosphamide) regimen provides a significant disease-free survival advantage over a conventionally dosed anthracycline-taxane sequence (LoE 1b B, AGO +/-) [14]. This treatment should be performed in experienced centers only.

All primary breast cancers should be tested for HER2 expression since detection of HER2 overexpression or gene amplification is a prerequisite for trastuzumab therapy. Thorough external and internal quality control for HER2 testing is strongly recommended. In HER2-positive disease, benefit for adjuvant trastuzumab therapy has been demonstrated for node-negative and node-positive patients. Registration studies only included node-negative patients with tumors > 1 cm. Yet, limited data suggests that patients with HER2-positive tumors < 1 cm also have a substantially increased risk of recurrence compared to those with HER2-negative disease [15]. Therefore, in patients with tumors > 5 mm and additional risk factors, who are candidates for adjuvant chemotherapy, the use of trastuzumab can be considered (LoE 4 C, AGO +). Based on the results of the registration trials, adjuvant trastuzumab may be used sequentially (LoE 2b B, AGO +) or concurrently with taxane chemotherapy. Recent evidence [16] suggests a substantial numerical advantage of concurrent use of trastuzumab with a taxane compared to sequential administration even though it is not significant after correction for multiple testing as stated in the study protocol. Thus, concurrent use (LoE 2b B, AGO +/-) of trastuzumab with taxane chemotherapy is preferable.

Neoadjuvant Chemotherapy / Primary Systemic Therapy

NACT is the current standard of care for patients with large, inoperable tumors or inflammatory disease. Several ran-

domized trials have demonstrated in operable breast cancer that anthracycline- and taxane-containing regimens were equally effective regardless of whether they were administered postoperatively or preoperatively. Moreover, tumor response in terms of pathologic complete remission (pCR) after preoperative chemotherapy may serve as a short-term surrogate marker for long-term outcome. This theory is supported by the favorable long-term outcome which has been shown consistently for patients who achieved a pCR after NACT. Anthracycline- and taxane-based chemotherapy regimens have been extensively studied in RCTs and are the most frequently applied regimens in the neoadjuvant setting. Young patients with negative hormone receptor status, poor grading, non-lobular tumor type, and triple-negative phenotype have a high chance of achieving a pCR [17]. In a recently published analysis of the Gepartrio trial [18], no evidence of a difference in response to NACT was found by tumor stage when adjusted for baseline characteristics. Data for response prediction by gene expression profiles are not sufficiently robust to recommend them for use in clinical practice. For neoadjuvant endocrine treatment, low ER expression, high Ki-67 (> 10%), and more advanced tumor stage were predictive for low sensitivity. Clinical examination, sonography, mammography, and MRI are possible methods of monitoring tumor response under NACT.

Adjuvant Endocrine Therapy

Prerequisites for adjuvant endocrine treatment are a valid determination of the menopausal status and a reliable test for endocrine sensitivity. Only patients with endocrine-responsive tumors should receive anti-hormonal treatment. As stated by the St. Gallen Consensus Panel, endocrine sensitivity is present if any tumor cells express either or both steroid hormone receptors (LoE 1a A, AGO +/-) [19–21].

Premenopausal Patients

Tamoxifen for 5 years is still considered standard endocrine therapy in all premenopausal women with endocrine sensitivity independent of prior adjuvant chemotherapy (LoE 1a A, AGO +/-). The role of ovarian ablation or suppression in addition to tamoxifen is still unclear [22, 23]; therefore, adjuvant gonadotropin-releasing hormone (GnRH) agonist therapy remains under active investigation (ongoing studies: SOFT = Suppression of Ovarian Function Trial; TEXT = Tamoxifen Exemestan trial). Chemotherapy followed by tamoxifen and 2–5 years GnRH agonists may be considered for certain subgroups (< 40 years; LoE 2a C, AGO +).

In cases of relevant contraindications against tamoxifen, GnRH agonists alone were discussed as an option, but are not recommended by the AGO. Aromatase inhibitors are not indicated in premenopausal patients, not even in combination with GnRH agonists, after chemotherapy-induced amenorrhea or if relevant contraindications against tamoxifen exist (LoE 5 D, AGO –) [24, 25]. In the case of deep vein thrombo-

sis, tamoxifen therapy accompanied by adequate anticoagulation may also be considered.

Since two RCTs were not able to show a significant effect, ovarian protection by GnRH agonists during chemotherapy cannot be recommended (LoE 1b B, AGO -) [26–29]. However, fertility preservation counseling is suggested in all patients who want to preserve their fertility (LoE 5 D, AGO +).

Postmenopausal Patients

Adjuvant endocrine treatment of postmenopausal women can be performed in different ways:

1. Sequential approach (AGO +/+): i) Tamoxifen for 2–3 years followed by an aromatase inhibitor for 3–2 years (LoE 1a A). Sequential aromatase inhibitor treatment up to 5 years is not evidence-based and may be given only in special situations (LoE 5 D, AGO +/-); ii) Aromatase inhibitor for 2–3 years followed by tamoxifen for 3–2 years (LoE1b C) with a preference for this approach in node-positive disease (data only available for letrozole).
2. Upfront aromatase inhibitor (AGO +): Aromatase inhibitor therapy upfront for 5 years (LoE 1a A, AGO +) is superior to tamoxifen for 5 years with regard to disease-free survival. In both trials with adequate follow-up (ATAC, BIG 1–98), a survival benefit was not shown [30]. In BIG 1–98, the censored analysis (patients who crossed from tamoxifen to letrozole were censored) suggests a significant survival advantage for letrozole [31]. Interpretation of these results, however, is difficult; therefore, upfront approaches can only be recommended with regard to reduction of recurrences (AGO +).
3. Standard treatment with tamoxifen 5 years: Tamoxifen 20 mg/day for 5 years is still a valid treatment option (LoE 1a A, AGO +). For patients treated with tamoxifen for 5 years, subsequent aromatase inhibitor therapy 3–5 years as extended endocrine treatment can be prescribed (extended adjuvant aromatase inhibitor therapy, EAT) (LoE 1b A, AGO +); in node-positive disease, a significant survival benefit was shown (LoE 2b B, AGO +/+). In a subgroup analysis, a substantial benefit of EAT was demonstrated also for patients who became postmenopausal during the 5 years of tamoxifen treatment (LoE 2b B, AGO +) [32].

Ongoing studies for postmenopausal patients with hormone receptor-positive tumors are PREFACE (translational research), COMPACT, and EVALUATE (compliance).

Bisphosphonates

In some studies, adjuvant bisphosphonate treatment in primary breast cancer shows an improvement of disease-free survival in individual studies, also for overall survival (LoE 1b C, AGO +). Evidence-based treatment options are clodronate (1,600 mg/day orally for 2 years) (LoE 1b, Gr B, AGO +), or zoledronate (5 mg intravenously every 6 months for 3 years),

in postmenopausal (LoE 3b C, AGO +) and in premenopausal patients (LoE 2b C, AGO +) [24, 33].

Adjuvant Radiotherapy

For both, adjuvant PMRT of the chest wall and radiotherapy of the breast after breast-conserving surgery, significant improvement of locoregional control as well as overall survival has been demonstrated [34, 35]. These benefits are independent and additive to those of adjuvant systemic therapies and, with regard to PMRT, even significant for patients with 1–3 tumor-infiltrated lymph nodes (pN1a) [36–42] (LoE1a A, AGO +). In contrast, the impact of PMRT in T3pN0 has been overestimated and seems to be marginal, particularly in patients who receive modern adjuvant systemic treatment (LoE 2b B, AGO +/-).

Modern radiotherapy should be based on CT-based treatment planning, electronic portal imaging devices etc. in order to improve accuracy and reproducibility of patient set-up, definition, and localization of clinical target volume as well as boost volume, homogeneity of dose distribution, and precision of set-up verification, although data from prospective trials or cohort studies are lacking. New concepts include: i) boost radiotherapy of the primary tumor region; ii) hypofractionation; iii) accelerated partial breast irradiation (APBI).

Pathological characteristics influencing local relapse after breast-conserving surgery or mastectomy have an important impact on application of radiotherapy [43]. A boost dose of 16 Gy significantly reduced the negative effects of both young age and high-grade invasive ductal cancer [44–46]. In DCIS, a minimal lesion-free margin of 2 mm should be obtained when breast-conserving surgery for DCIS is combined with radiotherapy [47–48].

Micrometastatic node positivity (pNmic) or isolated tumor cells in locoregional lymph nodes, known to be associated with poorer survival compared to pN0 disease, nowadays do not alter any indication for radiation therapy (LoE 2b B, AGO -/-) [49, 50]. Extracapsular tumor spread (ECS), which is not part of the TNM classification any more and only an optional information in the pathology report, and the risk of local, axillary, and supraclavicular recurrence in node-positive, premenopausal patients with breast cancer was investigated by the International Breast Cancer Study Group which came to the conclusion that the decision for additional regional radiotherapy should not be based solely on the presence of ECS (LoE 2b B, AGO -/-) [51]. The management of internal mammary nodes in breast cancer is controversial due to the lack of mature data. Two large randomized trials (French Group Trial (n = 1,334 patients), European Organization for Research and Treatment of Cancer (EORTC) Trial 22922 (n = 4,004 patients)) are currently evaluating the possible benefit of internal mammary irradiation. The updated

NCCN Practice Guidelines recommend radiotherapy to the internal mammary nodes if internal mammary lymph nodes are clinically or pathologically positive. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph node field (LoE 2b C, AGO +/-) [38, 52].

In the adjuvant situation, radiotherapy and trastuzumab can be given concomitantly (LoE 2b B, AGO +). Data from the North Central Cancer Treatment Group Phase III Trial N9831 as well as reports from mono-institutional studies show that concurrent adjuvant radiotherapy and trastuzumab for

early-stage breast cancer was not associated with increased acute adverse events. There was no excess of acute cardiotoxicity observed with the combination of left-sided internal mammary irradiation and concurrent trastuzumab. Further follow-up is required to assess late adverse events [53].

In a second chapter, in the next issue of *BREAST CARE*, we will publish the updated AGO recommendations on prevention, early detection, life style; premalignant lesion, DCIS; recurrent and metastatic breast cancer. The next update of the AGO recommendations for the diagnosis and treatment of early and metastatic breast cancer is planned for January 2011.

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