Update 2010 of the German AGO Recommendations for the Diagnosis and Treatment of Early and Metastatic Breast Cancer – Chapter B: Prevention, Early Detection, Lifestyle, Premalignant Lesions, DCIS, Recurrent and Metastatic Breast Cancer

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Introduction

For the last 9 years, the Breast Committee of the German Gynecological Oncology Group (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO) has published annually updated and evidence-based recommendations for the diagnosis and treatment of early and metastatic breast cancer. These guidelines are now 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 are made according to a well defined scale (AGO +/-; table 1). In addition, we have 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 prevention, early detection, lifestyle; premalignant lesion, ductal carcinoma in situ (DCIS); recurrent and metastatic breast cancer (table 1).

Early Detection, Prevention, Lifestyle Factors

Early Detection and Diagnosis

New evidence is available on ultrasound breast imaging in cases of dense breast tissue. A systematic review was published 2009 in BMC Cancer [3] about the benefits and risk of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. They neither found randomized controlled trials (RCTs) nor systematic reviews, but 6 cohort studies of intermediate level of evidence (LoE 3b). The authors conclude that supplemental breast ultrasound in cases of mammographically dense (American College of Radiology (ACR) type 3 and 4) tissue permits detection of small, otherwise occult, breast cancer in about 0.32%, but remind of potential adverse impacts as a consequence of an increased biopsy rate (LoE 3bB, AGO +).

A recent review of contrast-enhanced magnetic resonance imaging (CE-MRI) in preoperative cancer staging stated an estimate of additional cancer foci detection, occult in conventional imaging, of 16%. This changed surgical management, usually from breast conservation to more radical surgery.

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Advice on nutritional facts: Gabriele Stangl, Halle.

Table 1. AGO grades of recommendation, from Kommission ‘Mamma’ der Arbeitsgemeinschaft für Gynäkologische Onkologie e.V. (AGO) Guidelines 2010, Version 1.0; 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.

However, there was no evidence for improving the prognosis. Emerging data indicate that preoperative MRI does not reduce the re-excision rate but causes false-positive results. In conclusion, RCTs are recommended to establish the clinical, psychosocial, and outcome effects of MRI. One current RCT is ongoing (COMICE trial), but so far, results have only been reported in abstract form [4–5]. MRI increases detection of contralateral breast disease including both true-positives and false-positives. Most published studies do not include consecutive women and report on outcome, so their data were prone to selection bias [6]. None of the results on CE-MRI in preoperative staging of early stage breast cancer encourage its routine use in women with established breast cancer until ‘high levels of evidence demonstrate that preoperative MRI either improves surgical care, reduces the number of required surgeries or (more importantly) reduces at least local recurrence, if not distant metastases and death due to breast cancer’ (LoE 3b D, AGO +/-).

Breast Cancer Risk and Prevention

About 20% of breast cancers emerge on the basis of a genetic predisposition. Five percent of them are transmitted via a dominant monogenic trait. Mutation in the genes *BRCA1* and *BRCA2* are responsible for about 60% of these cases. The remaining cases may be due to rare high-penetrance genes and/or moderate/low-penetrance genes transmitted by a poly-genetic trait. Deleterious *BRCA* mutations confer an 80% lifetime risk for the development of breast and/or ovarian cancer and a 40–60% risk for the development of a second breast cancer on the contralateral side.

Based on the analysis of over 6,000 families, the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) has defined inclusion criteria for genetic testing that comprise families with a mutation detection probability of at least 10% (LoE 2b B, AGO ++). Moreover, an intensified surveillance program including mammography, ultrasound, and MRI is offered to women with deleterious *BRCA* mutations as well as to women with a non-informative or impractical genetic test and a lifetime risk of > 29% or a heterozygous risk of > 19% starting at the age of 25. Although the screening program allows the detection of early stage breast cancers (LoE 2a B, AGO ++), evidence for reduction of mortality is still lacking. Moreover, accumulating data suggest a spectrum bias of *BRCA*-associated tumors that may influence diagnos-

tic as well as therapeutic strategies. Therefore, intensified screening should only be offered within the GC-HBOC program that secures long-term follow-up.

Besides early detection, mutation carriers may opt for prophylactic surgery. While prophylactic bilateral salpingo-oophorectomy (PBSO) (LoE 2a B, AGO ++) and prophylactic bilateral mastectomy (PBM) (LoE 2a B, AGO +) lead to cancer-specific incidence and mortality reduction in healthy mutation carriers, overall mortality reduction is only convincingly reported for PBSO.

Standard surgical and adjuvant therapy is recommended for mutation carriers with primary breast cancer. PBSO (LoE 2b B, AGO +); tamoxifen (LoE 2b B, AGO +/-) may improve disease outcome. Insufficient data are available on the benefit of contralateral mastectomy (LoE 2b B, AGO +/-). Based on current results of the GC-HBOC, the decision should not only consider prognosis of the primary tumor but also age at onset and the affected gene.

Systemic therapy should be performed according to standard guidelines (LoE 2b B, AGO +). However, current research indicates that *BRCA*-associated tumors exhibit a therapeutic spectrum bias, i.e. different chemosensitivity and responsiveness to specific therapeutic molecules such as platinum-based agents and PARP inhibitors. Therefore, women with *BRCA*-associated tumors should be offered the chance to participate in ongoing therapeutic studies within the GC-HBOC, AGO-B, GBG, or WSG.

Lifestyle Factors

Modifiable lifestyle factors have been described to be of significant impact on the prognosis of breast cancer patients [7]. While maintaining normal body mass index (BMI) and increasing physical activity have been confirmed to have a favorable impact on prognosis in multiple trials, we recommend adherence to general nutrition guidelines which incorporate the complexity of dietary values (LoE 2a B, AGO +). A recent cohort analysis by Li et al. [8] utilized a population-based nested case control study design which enrolled 365 patients diagnosed with an estrogen receptor-positive (ER+) first primary invasive breast cancer and a second primary contralateral invasive breast cancer, and 726 matched controls diagnosed with only an ER+ first primary invasive breast cancer. Obesity, alcohol use, and smoking data were ascertained from medical record reviews and participant interviews. Using

conditional logistic regression, the authors evaluated associations between these 3 exposures and second primary contralateral breast cancer risk. Obesity, consumption of ≥ 7 alcoholic beverages per week, and current smoking were all positively related to risk of contralateral breast cancer (odds ratio (OR) 1.4, 95% confidence interval (CI) 1.0–2.1; OR 1.9, 95% CI 1.1–3.2; and OR 2.2, 95% CI 1.2–4.0, respectively). Compared with women who consumed fewer than 7 alcoholic beverages per week and were never or former smokers, women who consumed ≥ 7 drinks per week and were current smokers had a 7.2-fold (95% CI 1.9–26.5) elevated risk of contralateral breast cancer. We conclude that patients should be advised to optimize their lifestyle by normalizing their BMI, increase physical activity, and refrain from smoking and regular alcohol consumption (LoE 2b B, AGO –).

Premalignant Lesions, DCIS

Intraepithelial Neoplasms of the Breast with Uncertain Biological Potential (B3 Lesions)

Applying the histological B-classification to breast core biopsies, lesions of uncertain biological potential like atypical intraductal hyperplasia (ADH), flat epithelial atypia (FEA), and lobular intraepithelial neoplasia (LN/LIN) are classified together as B3. Also papillomata, radial scars, and phyllodes tumors are grouped into the B3 group [9]. In screening programs, 5–10% of histological diagnoses belong to the B3 category [10, 11]. The type of treatment in the case of a B3 diagnosis should be individually determined in an interdisciplinary discussion of the imaging findings and the pathology results [12, 13].

ADH (atypical intraductal proliferation, ductal intraepithelial neoplasia grade 1B; DIN1B) is defined as any intraductal architectural atypia with micropapillary or cribriform proliferations and non-high-grade nuclear atypia not exceeding 2 mm in diameter or 2 completely filled ducts. Proliferation exceeding 2 mm or 2 completely filled ducts has to be considered as intraductal carcinoma low-grade. ADH in core-/vacuum-assisted biopsy should be followed by an open excisional biopsy (LoE 3a C, AGO ++). When found at margins of resection specimens, no further surgery is required if ADH represents an incidental finding accompanying invasive or intraductal carcinoma (LoE 3a C, AGO ++). Women with ADH should be informed about their elevated risk of ipsi- and contralateral breast cancer (6–10 times at 10 years), and mammography at 12-month intervals is recommended (LoE 3a C, AGO ++). Medical prevention should only be offered after individual and comprehensive counseling; the net benefit strongly depends on risk status, age, and pre-existing risk factors for side effects (tamoxifen, raloxifene; LoE 1b A, AGO +). Study participation is recommended [14–22].

FEA (columnar cell hyperplasia with atypia; columnar cell metaplasia with atypia; ductal intraepithelial neoplasia grade

1A; DIN 1A) provides an atypical intraductal proliferation which is discriminated from ADH by architectural features (micropapillary, cribriform) and from clinging carcinoma by a low grade of nuclear atypia (G1 not G2/G3). FEA is frequently associated with calcifications and may be associated with intraductal carcinoma. Therefore, correlation with imaging is mandatory. When found in core biopsy, no further surgery will be required if calcifications are completely removed. If calcifications persist radiographically, guided vacuum-assisted biopsy may follow core biopsy (LoE 3a C, AGO ++). When found at margins of resection specimens, no further surgery is necessary as long as calcifications have been completely removed (LoE 3b C, AGO ++). Recommended intervals (24 months) of the mammography screening program need not be shortened [23–27].

LIN (atypical lobular hyperplasia, lobular carcinoma in situ, LCIS/CLIS) provides an incidental finding and is not suited to explain any radiographic abnormality. LIN is categorized as B3 as long as the criteria for pleomorphic LIN and LIN with necrosis or LIN with extensive involvement of lobules are not fulfilled. When LIN is found in core-/vacuum-assisted biopsy and correlation with imaging is not conclusive, open excisional biopsy should be performed since LIN is frequently associated with accompanying invasive cancer (LoE 2b C, AGO ++). Accordingly, LIN at margins of resection specimens does not require further surgery unless imaging abnormality persists or LIN is of the pleomorphic, necrotic, or extensive type (LoE 3a C, AGO ++). As with ADH, women with LIN should be informed about their elevated risk of ipsi- and contralateral breast cancer (7 times at 10 years) and should receive surveillance with reduced intervals of mammography (12 months) (LoE 3a C, AGO ++). With regard to antihormonal therapy, no differences to ADH exist (see above) [28–37].

DCIS

The main modification in comparison to last year's version is the adaptation of international standards with respect to the requirements for tumor-free margins. While in previous years, the commission adopted the data by Silverstein and Lagios et al. [38, 39] that showed inverse correlation of increased margin width with recurrence rate, newer data did not convincingly show that wide margins are a prerequisite for local safety, particularly together with application of modern treatment regimens. The latest Cochrane review [40] confirmed that radiotherapy added a statistically significant benefit to all ipsilateral breast events (hazards ratio (HR) 0.49, 95% CI 0.41–0.59; $p < 0.00001$) and ipsilateral DCIS recurrences (HR 0.64, 95% CI 0.41–1.01; $p = 0.05$). Pooled analysis for invasive recurrence did not reach statistical significance. Radiotherapy should therefore generally be added after breast conserving surgery (BCS) of DCIS. This is supported by the fact that the review could not identify long-term toxicity from use of radiotherapy (LoE 1a B AGO ++).

That in mind, the commission reviewed current data, hallmarked by the papers of Dunne et al. [41] and Jones et al. [42] and concluded that at least a free margin of more than 2 mm should be achieved (LoE 2b C AGO +). Using this modified approach, it should be possible to conserve many more breasts and avoid a substantial amount of re-excisions as compared to the previous recommendation that demanded re-excisions if the specimen revealed free margins of less than 10 mm.

Open Questions

These were thoroughly addressed during last year's NIH State-of-the-Science Conference. (consensus.nih.gov/2009/DCIS%20images/dcis_draftsmt.pdf) [43]. The most critical research questions have been identified. Amongst them the following ones are of particular clinical importance: i) Investigation and validation of combinations of new and existing clinical, pathologic, and molecular factors to better risk-stratify patients who have DCIS and thus identify the optimal therapy for each individual; ii) Further development of decision aids, along with their integration within clinical practice. Their impact on the quality of care for women who have DCIS should be investigated.

Recommended Studies

There are 2 recommended clinical trials active in Germany: i) IBIS2 – DCIS: Adjuvant Tamoxifen Compared With Anastrozole in Treating Postmenopausal Women With DCIS; and ii) GEC-ESTRO APBI TRIAL: Interstitial Brachytherapy Alone Versus External Beam Radiation Therapy After Breast Conserving Surgery for Low-Risk Invasive Carcinoma and Low-Risk DCIS of the Female Breast.

Recurrent and Metastatic Breast Cancer

Specific Sites of Metastasis

Metastasis from breast cancer can occur in any organ. In metastatic disease, systemic medication is the therapy of first choice (LoE 2a B, AGO ++). However, there are some clinical situations and specific sites of metastasis in which additional or alternative local procedures can be helpful and influence disease-free intervals. Surgery of metastases can be performed in the case of (solitary) persistence after systemic treatment, and in cases of pain and ulceration, where no further alternative modalities like radiotherapy, radiofrequency ablation, selective intraarterial radiotherapy (SIRT), cryotherapy or local chemotherapy exist (LoE 5 D, AGO +/-). Histological verification of the metastases should be performed before any local procedure. Observational studies demonstrated improved symptom-free survival rates following surgery of metastases in lung, liver, stomach, intestines, adrenals, ovaries, and uterus.

In retrospective studies, it was shown that the surgical excision of the primary breast tumor can prolong symptom-

free intervals in selected metastatic cases (LoE 4 C, AGO +/-).

Symptomatic malignant effusions in body cavities should be punctured and drained. In recurrent pleural effusions, thorascopic pleurodesis should be performed, and cardio-surgery can be useful in single patients. Intraabdominal installation of chemotherapy or bispecific antibodies like catumaxomab can reduce malignant ascites (LoE 3b D, AGO +/-). It should be performed in an in-patient setting in order to anticipate potential side effects. Antibody therapy in pleural effusion is still under investigation.

Locoregional Recurrence: The Role of Treatment

Locoregional recurrence of invasive breast cancer is defined by clinical and radiographic evaluation documenting recurrent disease confined to the chest wall, breast, and regional lymph nodes. Treatment options for locoregional recurrent breast cancer after heterogeneous prior treatment are limited. Increasing numbers of patients are treated with BCS followed by systemic therapy and radiotherapy. Failure rates after BCS increase by 1–2% per year as reported by large trials and even after mastectomy, local recurrence rates may be high, and 5-year overall survival rates amount to 65–50%. Multiple risk factors have been identified. Multivariate analysis stratified by treatment showed that age is an independent factor for local control. Tumor location, interval between surgery and radiotherapy, and boost technique influence local control after BCS. Hormone receptor expression and HER2 status are important predictors for efficacy of systemic therapy. Most women diagnosed with second cancer in a previously irradiated breast are advised to undergo mastectomy [44]. A limited number of publications have reported on patients outcome after second excision and radiation therapy. The best survival outcome was seen in patients with R0 resection, irradiation (hyperthermia), and endocrine therapy for ER+ tumors. Chemotherapy may be considered in individual patients. Emerging new therapeutic approaches using monoclonal antibody against HER2 have yielded improved survival.

Endocrine Treatment of Metastatic Breast Cancer

Endocrine therapy remains the most important approach for treatment of hormone-sensitive non-life-threatening metastatic breast cancer. Changes in receptor profiles are an important issue, since the molecular phenotype of the primary tumor is often used for treatment decisions in the metastatic setting. One prospective study, BRITS (Breast Recurrence In Tissue Study), investigated 137 matched primary and recurrent breast cancer tissue samples. A switch in receptor status, in either direction, was identified for ER in 10.2%, progesterone receptor (PR) in 24.8%, and HER2 in 2.9%, respectively. The switch led to a change in subsequent treatment in 24 patients (17.5%). This study strongly emphasizes that the management of locally recurrent or metastatic breast cancer

should include tissue sampling, since switches of ER, PR, or HER2 status in the breast cancer recurrence may change the planned treatment for 1 in 6 patients [45].

No changes in treatment recommendations for endocrine treatment of metastatic breast cancer in premenopausal women were made.

In postmenopausal women with advanced (metastatic) breast cancer, aromatase inhibitors including those in current clinical use show a survival benefit when compared to other endocrine therapy. This is demonstrated in many clinical trials and confirmed in a Cochrane meta-analysis updated in 2009 [46].

Fulvestrant in the approved dose of 250 mg every 4 weeks is not superior to aromatase inhibitors or tamoxifen as first line or second line treatment of metastatic breast cancer [47, 48]. However, one trial ('CONFIRM') so far only published as an oral presentation at the San Antonio Breast Cancer Symposium 2009, suggests that a dose of 500 mg every 4 weeks is superior to 250 mg every 4 weeks with regard to progression-free survival [49]. One trial ('FIRST') using the higher dose of 500 mg every 4 weeks (HD) stated that first-line fulvestrant HD was at least as effective as anastrozole regarding the clinical benefit rate (primary end point) and overall response rate, and was associated with significantly longer time to progression (a secondary end point) [50]. However, in early 2010, the dose of 500 mg every 4 weeks was approved. Despite convincing preclinical data supporting the combined therapy strategy of fulvestrant plus an aromatase inhibitor, the prospective, randomized study 'FACT' presented also at the San Antonio Breast Cancer Symposium 2009 did not demonstrate any advantage by adding fulvestrant to anastrozole, and therefore this combination cannot be recommended [51].

Evidence suggests that switching from a non-steroidal to a steroidal aromatase inhibitor is as effective as fulvestrant in its approved dose of 250 mg every 4 weeks (study 'EFFECT') [52]. It seems likely that also the switch from a steroidal to a non-steroidal aromatase inhibitor is effective and is therefore a therapeutic option.

Several lines of evidence support the hypothesis that HER2-positive breast cancer is associated with endocrine resistance. The addition of trastuzumab or lapatinib to aroma-

tase inhibitor treatment is able to enhance efficacy over endocrine treatment alone [53–55]. However, given the relatively short progression-free interval in the phase III trials with indirect comparison to those observed in trials with chemotherapy, we recommend to consider chemotherapy in HER2-positive patients.

Targeted Agents

Use of targeted drugs is standard in the treatment of metastatic breast cancer. In the case of progression during trastuzumab therapy, change of chemotherapy partner (LoE 1b B, AGO +), use of lapatinib with capecitabine (LoE 1b B, AGO +), and combination of lapatinib with trastuzumab (particularly for heavily pretreated patients; LoE 2b B, AGO +) are considered as clinically relevant therapy options.

The combination of lapatinib or trastuzumab with an aromatase inhibitors showed a statistically significant, but clinically only marginal benefit; therefore these combinations are regarded as an option; however, the combination with chemotherapy should always be considered in these high-risk patients (LoE 2b B, AGO +/-).

With regard to the use of bevacizumab in combination with second line chemotherapy, the best effect was shown with a taxane (LoE 1b B, AGO +), less clear with capecitabine (LoE 1b B, AGO +/-), and not visible or even with an apparently adverse effect with gemcitabine or vinorelbine (LoE 1b B, AGO -).

The compounds Rad001 (Everolimus), sorafenib, and sunitinib are approved for other oncologic indications. Currently, use of these drugs in breast cancer is not recommended outside of clinical trials (LoE 2b B, AGO -). In Germany, patients can be included in one of the following studies: RADAR (Rad001), MADONNA (sorafenib).

In the first chapter (Chapter A), published in the last issue of Breast Care, we published the updated AGO recommendations on surgery, pathology and prognostic factors, adjuvant and neoadjuvant therapy, adjuvant radiotherapy. 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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